

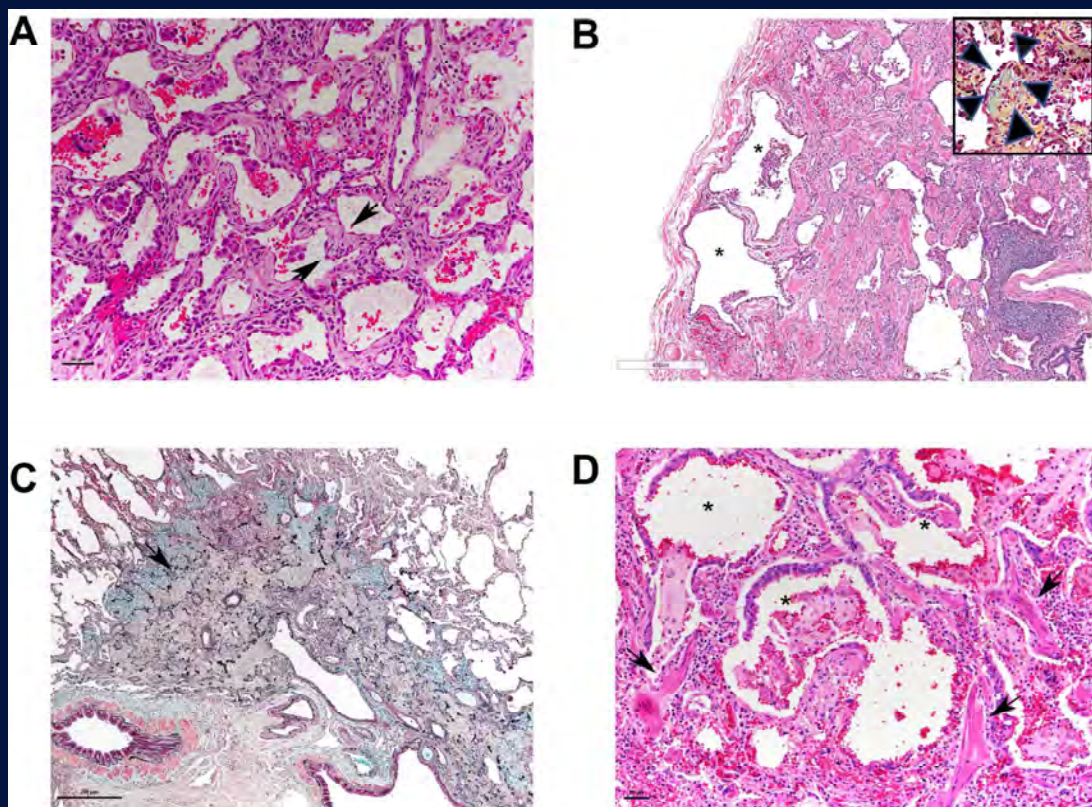
Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

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**1ª associação
LABA/LAMA/ICS**
indicada na ASMA⁴
Dose fixa diária¹

1 vez dia¹

**Zimbus[®]
breezhaler[®]**

Indacaterol, glicopirrônio, furoato de mometasona
pó para inalação, cápsulas

**NOVA
ASSOCIAÇÃO
LABA/LAMA
/ICS¹**

Dá ritmo à vida^{2,3}

Para adultos com ASMA moderada a grave não controlados adequadamente com LABA/ICS.¹

1. Zimbus[®] Breezhaler[®], Resumo das Características do Medicamento, última atualização 12/11/2021. Disponível em https://www.ema.europa.eu/en/documents/product-information/zimbus-breezhaler-epar-product-information_pt.pdf. Consultado a 12/01/2022. Terapêutica inalada, 1x/dia, combinação de dose-fixa de acetato de indacaterol, brometo de glicopirrônio e furoato de mometasona. Mistura de lactose em pó para inalação, doses únicas, através do dispositivo BREEZHALER[®] que permite a confirmação de doses¹. *Entende-se por 'dá ritmo à vida' que o doente ao tomar Zimbus[®] Breezhaler[®] poderá obter melhorias de função pulmonar, controlo de sintomas, qualidade de vida e redução de exacerbações vs terapêuticas padrão. 2. Gessner C, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med. 2020 Aug-Sep;170:106021. 3. Kerstjens HAM, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. Lancet Respir Med. 2020 Oct;8(10):1000-1012. 4. EPAR: European public assessment report. https://www.ema.europa.eu/en/documents/assessment-report/zimbus-breezhaler-epar-public-assessment-report_en.pdf; consultado em 21/05/2021. LABA: Agonista Beta2 de longa duração de ação; LAMA: antagonista muscarínico de longa duração de ação; ICS: corticosteroides inalados.

Zimbus Breezhaler 114 microgramas/46 microgramas/136 microgramas pó para inalação, cápsulas

NOTA: Antes de prescrever consulte o RCM do medicamento. **APRESENTAÇÃO:** Pó para inalação, cápsula (pó para inalação). Cada cápsula contém 150 microgramas de indacaterol, 50 microgramas de glicopirrônio e 160 microgramas de furoato de mometasona. Cada dose libertada (a dose libertada através do aplicador bucal do inalador) contém 114 microgramas de indacaterol (na forma de acetato), 8 microgramas de brometo de glicopirrônio equivalente a 46 microgramas de glicopirrônio e 136 microgramas de furoato de mometasona. **Excipiente(s) com efeito conhecido:** Cada cápsula contém 25 mg de lactose mono-hidratada. **INDICAÇÕES:** Zimbus Breezhaler está indicado como terapêutica de manutenção da asma em doentes adultos não controlados adequadamente com uma associação de um agonista beta₂ de ação prolongada e uma dose alta de corticosteroide inalado em regime de manutenção que experimentaram uma ou mais exacerbações da asma no ano anterior. **POSOLOGIA: Adultos:** A dose recomendada é uma cápsula inalada uma vez por dia. A dose máxima recomendada é de 114 µg/46 µg/136 µg uma vez por dia. **Doentes pediátricos (< 18 anos):** Não recomendado em doentes com menos de 18 anos de idade. **Populações especiais: População idosa:** Não é necessário ajuste de dose em doentes idosos (65 anos de idade ou mais). **Compromisso renal:** Não é necessário ajuste de dose em doentes com compromisso renal ligeiro a moderado. Deve ter-se precaução em doentes com compromisso renal grave ou doença renal terminal que necessitem de diálise. **Compromisso hepático:** Não é necessário ajuste de dose em doentes com compromisso hepático ligeiro a moderado. Não existem dados disponíveis sobre a utilização deste medicamento em doentes com compromisso hepático grave, como tal deve ser utilizado nestes doentes apenas se o benefício esperado superar o risco potencial. **Modo de administração:** Apenas para utilização por via inalatória. As cápsulas não podem ser engolidas. Os doentes que não sintam melhorias na sua respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. As cápsulas têm de ser administradas usando apenas o inalador Zimbus Breezhaler. O tratamento deve ser administrado à mesma hora do dia todos os dias. Pode ser administrado independentemente da hora do dia. Após a inalação, os doentes devem lavar a boca com água sem engolir. Se for omitida uma dose, esta deve ser tomada assim que possível. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas de Zimbus Breezhaler devem ser sempre conservadas no blister para proteger da luz e humidade, e só podem ser removidas do blister imediatamente antes da utilização. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS/PRECAUÇÕES:** ♦ **Asma Aguda:** não deve ser utilizado para tratar sintomas agudos de asma, incluindo episódios agudos de broncoespasmo, para os quais é necessário um broncodilatador de curta ação. ♦ **Hipersensibilidade:** Se ocorrer uma reação de hipersensibilidade, Zimbus Breezhaler deve ser descontinuado imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Broncoespasmo paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncoespasmo paradoxal, o qual pode colocar a vida em risco. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Efeitos cardiovasculares:** Tal como outros medicamentos contendo agonistas adrenérgicos beta₂, este medicamento pode produzir um efeito cardiovascular clinicamente significativo em alguns doentes conforme avaliado através de aumentos na frequência cardíaca, pressão arterial e/ou sintomas, alterações do electrocardiograma (ECG). Este medicamento deve ser usado com precaução em doentes com patologias cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão, suspeita ou confirmação de prolongamento do intervalo QT, distúrbios convulsivos ou tirotóxicose e em doentes com resposta aumentada aos agonistas adrenérgicos beta₂). ♦ **Hipocalcemia:** Os agonistas adrenérgicos beta₂ podem causar uma hipocalcemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocalcemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. ♦ **Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos beta₂ e corticosteroides pode produzir um aumento da glicose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glicose plasmática deve ser monitorizada mais cuidadosamente. ♦ **Efeitos anticolinérgicos:** Tal como com outros medicamentos anticolinérgicos, este medicamento deve ser utilizado com precaução em doentes com glaucoma de ângulo fechado ou retenção urinária. ♦ **Doentes com compromisso renal grave:** Nos doentes com compromisso renal grave (taxa de filtração glomerular estimada inferior a 30 ml/min/1,73 m²), incluindo aqueles com doença renal terminal que necessitam de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. ♦ **Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *Candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após inalarem a dose prescrita. ♦ **Efeitos sistémicos dos corticosteroides:** Podem ocorrer efeitos sistémicos dos corticosteroides inalados, principalmente no caso de doses elevadas prescritas por períodos prolongados. Os efeitos sistémicos possíveis podem incluir: síndrome de Cushing, manifestações Cushingóides, supressão adrenal, atraso do crescimento em crianças e adolescentes, diminuição da densidade mineral óssea, cataratas, glaucoma e, mais raramente, uma série de efeitos psicológicos ou comportamentais incluindo hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão ou agressão (especialmente em crianças). Como tal, é importante que a dose de corticosteroide inalado seja titulada para a dose mais baixa na qual o controlo efetivo da asma é mantido. Podem ser notificados distúrbios visuais como o uso de corticosteroides sistémicos ou tópicos (incluindo intranasais, inalados ou intraculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento a um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a coriorretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. ♦ **Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. ♦ **Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. ♦ **Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos beta₂, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES:** ♦ **Bloqueadores adrenérgicos beta:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização. ♦ **Medicamentos conhecidos por prolongarem o intervalo QTc:** este medicamento deve ser administrado com precaução a doentes que estejam a ser tratados com inibidores da monoamina oxidase, antidepressivos tricíclicos ou medicamentos conhecidos por prolongar o intervalo QT. ♦ **Tratamento hipocalcémico:** O tratamento hipocalcémico concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico dos agonistas adrenérgicos beta₂. ♦ **Interação com inibidores do CYP3A4 e da glicoproteína P:** A inibição do CYP3A4 e da glicoproteína P (gp-P) não tem impacto na segurança de doses terapêuticas de Zimbus Breezhaler. ♦ **Outros antimuscarínicos de ação prolongada e agonistas adrenérgicos beta de ação prolongada:** A coadministração deste medicamento com outros medicamentos contendo antagonistas muscarínicos de ação prolongada ou agonistas adrenérgicos beta₂ de ação prolongada não foi estudada e não é recomendada. ♦ **Cimetidina ou outros inibidores do transporte de catiões orgânicos:** Não é esperada qualquer interação medicamentosa clinicamente relevante. **EFEITOS INDESEJÁVEIS:** ♦ **Frequentes (≥1% a <10%) e potencialmente graves:** hipersensibilidade. ♦ **Muito frequentes:** asma (exacerbação), nasofaringite. ♦ **Frequentes (≥1% a <10%):** infeção do trato respiratório superior, candidíase, infeção do trato urinário, cefaleia, taquicardia, dor orofaríngea, tosse, disfonia, gastroenterite, dor musculoesquelética, espasmos musculares, piroxíria. ♦ **Pouco frequentes (≥0,1% a <1%):** hiperglicemia, cataratas, boca seca, erupção cutânea, prurido, disúria. Para mais informações, consultar o titular de autorização de introdução no mercado ou o representante local do titular de autorização de introdução no mercado. Medicamento sujeito a receita médica. **Escala de comparticipação:** Escalão B. **Titular da AIM:** Novartis Europharm Limited. **Representante local:** Laboratório Medinfar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, N.º 29, Venda Nova, 2700-451 Amadora. Informações Essenciais Compatíveis com o Resumo das Características do Medicamento (ZIM_RCM20210422_IEC_v2).



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Editorial

Bem-vindos!

Nesta edição, destaca-se um conjunto de artigos de elevada relevância clínica e científica na área da Medicina Respiratória.

Em primeiro plano, um estudo com mais de 30 mil adultos com asma nos EUA revela que a não adesão medicamentosa por razões económicas permanece comum e está fortemente associada a piores desfechos, como agudizações e recursos aos serviços de urgência. Os autores sugerem que as reformas no sistema de saúde, como o Affordable Care Act e o Inflation Reduction Act, poderão contribuir para uma melhoria gradual na acessibilidade ao tratamento.

Na área da DPOC, um editorial e estudos originais complementares analisam o impacto dos corticosteroides inalados na prevenção de eventos cardiovasculares. Embora estes reduzam agudizações e declínio funcional, os dados disponíveis não mostram uma redução consistente nos eventos cardiovasculares maiores (MACE). No entanto, é sugerido um efeito protetor sobre a insuficiência cardíaca, com limitações inerentes aos estudos observacionais.

Outro destaque é o aumento significativo da proporção de pneumonia adquirida na comunidade atribuída a *Streptococcus pneumoniae* — sobretudo ao serotipo 3 — nas últimas duas décadas. Este achado levanta sérias questões quanto à eficácia das vacinas atuais e reforça a necessidade de estratégias vacinais mais abrangentes, nomeadamente com as novas vacinas conjugadas.

Na área da alergologia pediátrica, três artigos dão suporte robusto à implementação sistemática de programas de desclassificação, ou seja, retirada de diagnósticos não confirmados de alergia a penicilina em crianças e jovens. As evidências mostram que a maioria dos rótulos de alergia são incorretos e que o uso criterioso de testes de provocação medicamentosa, é seguro e eficaz.

Completam esta edição temas de elevada atualidade como o suporte respiratório não invasivo em cuidados paliativos pediátricos, a influência de fatores sociais na sibilância infantil e o início precoce da fibrose pulmonar.

Desejamos a todos uma leitura proveitosa e inspiradora, com impacto direto na prática clínica e na melhoria dos cuidados aos doentes com patologia respiratória.

Boas leituras!

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Informações essenciais compatíveis com o Resumo das Características do Medicamento

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Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes. **População pediátrica:** Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC. **Modo de administração:** Utilização por via inalatória. **Instruções de utilização:** Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do recipiente pressurizado a alta velocidade. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes devem ser instruídos sobre a técnica de inalação correta. É importante instruir o doente para: Ler com atenção as instruções de utilização no folheto informativo, que se encontra dentro da embalagem de cada inalador. Não utilizar o inalador se o agente excicante, contido na bolsa de alumínio, tiver vazado da sua embalagem. Preparar o inalador agitando-o e acionando-o quatro vezes para o ar antes da primeira utilização ou duas vezes quando o inalador não tenha sido utilizado há mais de sete dias, tenha sido exposto a temperaturas baixas ou tenha caído. Para obter uma deposição pulmonar adequada das substâncias ativas, o carregamento da dose tem de ser coordenado com a inalação. Doentes com dificuldade em coordenar o carregamento da dose com a inspiração podem utilizar Bevespi Aerosphere com uma câmara expansora para garantir a administração adequada do produto. Foi demonstrada compatibilidade com a câmara expansora Aerochamber Plus Flow-Vu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Não indicado para utilização em situações agudas. Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasma, isto é, como terapêutica de alívio. **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasma paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasma paradoxal, o qual pode colocar a vida em risco. Se ocorrer broncospasma paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrónio ou formoterol. Bevespi Aerosphere deve ser utilizado com precaução em doentes com doenças cardiovasculares graves, tais como cardiopatia isquémica, taquiarritmias ou insuficiência cardíaca grave. Recomenda-se também precaução em doentes com tireotoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito. **Hipocalcemia:** Os agonistas β_2 -adrenérgicos podem causar hipocalcemia significativa, o que pode aumentar a suscetibilidade para arritmias cardíacas. A diminuição do potássio sérico é normalmente transitória, não necessitando de suplementação. Em doentes com DPOC grave, a hipocalcemia pode ser potenciada por hipoxia e tratamento concomitante. **Hiperglicemia:** A inalação de doses elevadas de agonistas β_2 -adrenérgicos pode provocar o aumento da glucose plasmática. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, Bevespi Aerosphere deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. **Doentes com compromisso renal grave:** Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com Bevespi Aerosphere se o benefício esperado superar o risco potencial. **Doentes com compromisso hepático grave:** Em doentes com compromisso hepático grave, Bevespi Aerosphere só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** O potencial para interações metabólicas é considerado baixo. Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** **Outros antimuscarínicos e simpaticomiméticos:** A coadministração de Bevespi Aerosphere com outros medicamentos contendo anticolinérgicos e/ou agonistas β_2 -adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β_2 -adrenérgicos inalados. Não existe evidência clínica de interações quando utilizado concomitantemente com outros medicamentos para a DPOC, incluindo broncodilatadores β_2 -adrenérgicos de curta duração de ação, metilxantinas e esteroides orais e inalados. **Hipocalcemia induzida por fármacos:** O tratamento concomitante com derivados da metilxantina, esteroides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico inicial dos agonistas β_2 -adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante. **Bloqueadores β -adrenérgicos:** Os bloqueadores β -adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β_2 -adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β -adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β -adrenérgicos (incluindo colírios), dá-se preferência a bloqueadores β -adrenérgicos cardiosseletivos, embora também estes devam ser administrados com precaução. **Outras interações farmacodinâmicas:** Bevespi Aerosphere deve ser administrado com precaução em doentes que estejam a ser tratados com medicamentos conhecidos por prolongar o intervalo QTc. **Fertilidade, gravidez e aleitamento:** **Gravidez:** Não existem dados sobre a utilização de Bevespi Aerosphere em mulheres grávidas. Bevespi Aerosphere só deve ser utilizado durante a gravidez se os benefícios esperados superarem os potenciais riscos. **Amamentação:**

Não é conhecido se o glicopirronio ou o formoterol são excretados no leite humano. A administração de Bevespi Aerosphere a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para o bebé. **Fertilidade:** Considera-se pouco provável que Bevespi Aerosphere, administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** *Frequentes:* Ansiedade, Cefaleia, Tonturas, Boca seca, Náuseas, Espasmos musculares, Infecção do trato urinário, Dor torácica. *Pouco frequentes:* Reações de hipersensibilidade, incluindo erupção cutânea e prurido, Hiperglicemia, Agitação, Irrequietude, Insônia, Tremor, Taquicardia, Palpitações. Arritmias cardíacas (fibrilhação auricular, taquicardia supraventricular e extra-sístoles), Retenção urinária. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoam> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351217987373; Linha do Medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em outubro 2023. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de participação no regime geral e 84% de participação no regime especial). Versão 2.0 (outubro 2023).**

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Isto corresponde a uma dose calibrada de 5,3 µg de fumarato de formoterol di-hidratado, 9,6 µg de brometo de glicopirronio, equivalente a 7,7 µg de glicopirronio e 170 µg de budesonida. **Indicações terapêuticas:** Riltrava Aerosphere é indicado como tratamento de manutenção em doentes adultos com DPOC moderada a grave, que não estão adequadamente tratados com uma associação de um corticosteroide inalado e um agonista beta2 de longa duração de ação ou uma associação de um agonista beta2 de longa duração de ação e um antagonista muscarínico de longa duração de ação. **Posologia e modo de administração:** *Posologia:* A dose recomendada é máxima de 2 inalações 2x/dia (2 inalações de manhã e 2 inalações à noite). Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não se deve tomar uma dose a dobrar para compensar uma dose esquecida. *Populações especiais:* **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, apenas se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso hepático grave, o medicamento deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. **População pediátrica:** Não existe utilização relevante deste medicamento em crianças e adolescentes (com idade inferior a 18 anos) para a indicação da DPOC. **Modo de administração:** Para utilização por via inalatória. **Instruções de utilização:** De forma a assegurar uma administração correta do medicamento, o médico ou outro profissional de saúde deve demonstrar ao doente como utilizar corretamente o inalador, e deve monitorizar regularmente a técnica de inalação do doente. O doente deve ser aconselhado a ler com atenção o Folheto Informativo e seguir as instruções de utilização conforme indicado no mesmo. Ao acionar Riltrava Aerosphere, um volume de suspensão é expelido do recipiente pressurizado. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes que têm dificuldade em coordenar o acionamento com a inalação podem utilizar Riltrava Aerosphere com uma câmara expansora para garantir a administração adequada do medicamento. Pode ser utilizado com câmaras expansoras incluindo o Aerochamber Plus ou FlowVu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Não indicado para utilização em situações agudas. Este medicamento não é indicado para o tratamento de episódios agudos de broncospasmo, isto é, como terapêutica de alívio. **Broncospasmo paradoxal:** A administração de formoterol/glicopirronio/budesonida pode produzir broncospasmo paradoxal com sibilos e dispnéia imediatamente após a administração e pode ser potencialmente fatal. O tratamento com este medicamento deve ser imediatamente interrompido se ocorrer broncospasmo paradoxal. O doente deve ser avaliado e instituído tratamento alternativo, se necessário. **Deterioração da doença:** Recomenda-se que o tratamento com este medicamento não seja interrompido abruptamente. Se os doentes não considerarem o tratamento eficaz, devem manter o tratamento, mas tem de se procurar aconselhamento médico. O aumento da utilização de broncodilatadores de alívio indica um agravamento do quadro clínico subjacente e justifica uma reavaliação da terapêutica. A deterioração rápida e progressiva nos sintomas da DPOC é potencialmente fatal e o doente deve ser submetido a avaliação médica urgente. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas, p.ex. fibrilhação auricular e taquicardia, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirronio e formoterol. Este medicamento deve ser utilizado com precaução em doentes com doença cardiovascular grave não controlada e clinicamente significativa, tal como cardiopatia isquémica instável, enfarte agudo do miocárdio, cardiomiopatia, arritmias cardíacas, e insuficiência cardíaca grave. Recomenda-se também precaução ao tratar doentes com prolongamento do intervalo QTc (QTc > 450 milissegundos para homens ou > 470 milissegundos para mulheres), conhecido ou suspeito, quer seja congénito ou induzido por medicamentos. **Efeitos sistémicos com corticosteroides:** Podem ocorrer efeitos sistémicos com qualquer corticosteroide inalado, particularmente em doses elevadas prescritas por longos períodos de tempo. Estes efeitos são muito menos prováveis de ocorrer com o tratamento por inalação do que com corticosteroides orais. Os efeitos sistémicos possíveis incluem síndrome de Cushing, manifestações Cushingoides, supressão suprarrenal, diminuição da densidade mineral óssea, cataratas e glaucoma. Devem ser considerados efeitos potenciais na densidade óssea especialmente com a administração de doses elevadas durante longo período de tempo em doentes com fatores de risco coexistentes para osteoporose. **Perturbações visuais:** Podem ser notificadas perturbações visuais com a utilização sistémica e tóxica de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser encaminhado para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, tais como CRSC, que foram notificadas após a utilização de corticosteroides sistémicos e tópicos. **Transferência de terapêutica oral:** Recomenda-se atenção especial nos doentes que fazem a transição de esteroides orais, uma vez que podem continuar em risco de compromisso da função suprarrenal durante um período de tempo considerável. Os doentes que necessitam de terapêutica com doses elevadas de corticosteroides ou tratamento prolongado com a dose mais elevada recomendada de corticosteroides inalados, podem estar igualmente em risco. Estes doentes podem apresentar sinais e sintomas de insuficiência suprarrenal quando expostos a stress grave. Deve ser considerada cobertura adicional com corticosteroides sistémicos durante períodos de stress ou cirurgia eletiva. **Pneumonia em doentes com DPOC:** Tem sido observado um aumento na incidência de pneumonia, incluindo pneumonia que requer hospitalização, nos doentes com DPOC a receberem corticosteroides inalados. Existe alguma evidência de risco aumentado de pneumonia com o aumento da dose de esteroide, não tendo sido demonstrado de forma conclusiva nos diversos estudos. Não existe evidência clínica conclusiva para diferenças dentro da mesma classe na magnitude do risco de pneumonia entre os medicamentos contendo corticosteroides inalados. Os médicos devem continuar alerta para o possível desenvolvimento de pneumonia em doentes com DPOC pois as características clínicas de tais infeções sobrepõem-se aos sintomas das exacerbações da DPOC. Os fatores de risco para pneumonia em doentes com DPOC incluem tabagismo atual, idade avançada, IMC baixo e DPOC grave. **Hipocalcemia:** A hipocalcemia potencialmente grave pode resultar da terapêutica com agonistas-β. Estes têm o potencial de produzir acontecimentos cardiovasculares adversos. Recomenda-se precaução especial na DPOC grave, pois esse efeito pode ser potencializado pela hipoxia. A hipocalcemia também pode ser potencializada pelo tratamento concomitante com outros medicamentos que podem induzir hipocalcemia, tais como derivados de xantinas, esteroides e diuréticos. **Hiperglicemia:** A inalação de doses elevadas de agonistas β-adrenérgicos pode provocar o aumento da glicose plasmática. A glicemia deve ser monitorizada durante o tratamento de acordo com as orientações estabelecidas para doentes com diabetes. **Condições coexistentes:** Este medicamento deve ser utilizado com precaução em doentes com tirotoxicose. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, este medicamento deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. Os doentes devem ser informados sobre os sinais e sintomas do glaucoma de ângulo fechado e devem ser informados para interromper a utilização deste medicamento e contactar o seu médico imediatamente, caso algum destes sinais ou sintomas se desenvolvam. Não é recomendada a administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos. **Compromisso renal:** Como o glicopirronio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com este medicamento se o benefício esperado superar o risco potencial. **Compromisso hepático:** Em doentes com compromisso hepático grave, este medicamento só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** Prevê-se que o tratamento em associação com inibidores potentes do CYP3A, por exemplo itraconazol, cetoconazol, inibidores de protease do VIH e medicamentos que contêm cobistatado, aumente o risco de efeitos indesejáveis sistémicos, e deve ser evitado, a não ser que o benefício seja superior ao risco aumentado de reações adversas aos corticosteroides sistémicos, nesse caso os doentes devem ser monitorizados para reações adversas aos corticosteroides sistémicos. Este facto é de relevância clínica limitada em tratamentos de curta duração (1-2 semanas). Como o glicopirronio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** **Outros antimuscarínicos e simpaticomiméticos:** A administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos e/ou agonistas β-adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β-adrenérgicos inalados. A utilização concomitante de outros medicamentos beta-adrenérgicos pode ter efeitos potencialmente aditivos; portanto é necessário precaução quando outros medicamentos beta-adrenérgicos são prescritos concomitantemente com formoterol. **Hipocalcemia induzida por medicamentos:** A hipocalcemia pode aumentar a disposição para arritmias em doentes que são tratados com glicosídeos digitálicos. **Bloqueadores β-adrenérgicos:** Os bloqueadores β-adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito do formoterol. O uso simultâneo de bloqueadores β-adrenérgicos deve ser evitado, a não ser que o benefício esperado ultrapasse o risco potencial. Se forem necessários bloqueadores β-adrenérgicos, dá-se preferência a bloqueadores β-adrenérgicos cardioseletivos. **Outras interações farmacodinâmicas:** O tratamento concomitante com quinidina, disopiramida, procainamida, anti-histamínicos, inibidores da monoamina oxidase, antidepressivos tricíclicos e fenotiazinas pode prolongar o intervalo QT e aumentar o risco de arritmias ventriculares. Além disso, L-dopa, L-tirosina, oxitocina e álcool podem prejudicar a tolerância cardíaca aos beta-2-simpaticomiméticos. O tratamento concomitante com inibidores da monoamina oxidase, incluindo medicamentos com propriedades semelhantes como furazolidona e procabazina, pode dar origem a reações hipertensivas. Existe um risco elevado de arritmias em doentes a receberem anestesia concomitante com hidrocarbonetos halogenados. **Fertilidade, gravidez e aleitamento:** A administração deste medicamento a mulheres grávidas só deve ser considerada se o benefício esperado para a mãe justificar o potencial risco para o feto. A administração deste medicamento a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para a criança. Considera-se pouco provável que este medicamento administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** *Frequentes:* Candidíase oral; Pneumonia; Hiperglicemia; Ansiedade; Insônia; Cefaleia; Palpitações; Disfonia; Tosse; Náuseas; Espasmos musculares; Infecção do trato urinário. *Pouco frequentes:* Hipersensibilidade; Depressão; Agitação; Irrequietude; Nervosismo; Tonturas; Tremor; Angina de peito; Taquicardia; Arritmias cardíacas (fibrilhação auricular, taquicardia supraventricular e extrasístoles); Irritação da garganta; Broncospasmo; Boca seca; Equimose; Retenção urinária; Dor torácica. *Muito raras:* Sinais ou sintomas de efeitos sistémicos de glucocorticóides, por exemplo supressão suprarrenal; Comportamento anormal. **Desconhecida:** Angioedema; Visão turva; Cataratas; Glaucoma. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoam> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351 21 798 73 73; Linha do medicamento: 800 222 444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em abril 2022. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de participação no regime geral e 84% de participação no regime especial). Versão 1.1 (abril 2022).**

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Não adesão ao tratamento medicamentoso devido a custos entre pessoas com asma nos Estados Unidos: descobertas que reforçam a relevância da história e da reforma nos cuidados de saúde

Emily L. Graul,¹ Christer Janson²

A asma afeta mais de 20 milhões (8%) de adultos nos Estados Unidos (EUA) a cada ano.^{1,2} Assim como em muitas condições crônicas, o mau controle da asma pode ser atribuído à baixa adesão ao tratamento medicamentoso e à redução da qualidade de vida, resultando num peso elevado para o sistema de saúde e a economia.^{3,4} A não adesão aos medicamentos devido aos custos é um fator importante, pois as pessoas enfrentam grandes barreiras financeiras para acessar os cuidados de saúde nos EUA, além do próprio impacto financeiro da condição crônica. Os medicamentos prescritos representam uma parte significativa dos custos relacionados às doenças crônicas nos EUA, particularmente cerca de ~50% dos gastos com asma.⁴

Esforços para reduzir a não adesão medicamentosa relacionada a custos não só diminuem o fardo financeiro no sistema de saúde dos EUA, mas também ajudam as pessoas a melhorar os sintomas da doença. Pesquisas recentes têm explorado a não adesão medicamentosa relacionada aos custos em pessoas com doenças crônicas, como doenças cardíacas coronárias,⁵ doenças hepáticas⁶ e doença pulmonar obstrutiva crônica (DPOC),⁷ mas deram menos atenção à asma.

Neste contexto, nesta edição da revista *Thorax* com artigos do *Archives Disease in Childhood*, Hung et al.⁸ abordam essa lacuna no conhecimento ao realizar um estudo que investiga o impacto da não adesão medicamentosa relacionada a custos numa amostra representativa de 30.793 pessoas com asma ativa nos EUA. Utilizando dados de questionários do National Health Interview Survey (NHIS) de 2011 a 2022, os autores analisaram as tendências anuais na prevalência da não adesão medicamentosa relacionada a custos, os fatores associados e a relação entre esta condição e eventos adversos relacionados à asma, como visitas ao serviço de urgência e exacerbações. Uma pessoa foi considerada como tendo não adesão medicamentosa relacionada a custos se relatou ter omitido doses de medicamentos, reduzido o uso ou atrasado o reabastecimento

de medicamentos no último ano para poupar dinheiro, definição consistente com estudos anteriores.^{5,7}

Uma tendência decrescente na prevalência da não adesão medicamentosa relacionada a custos foi observada ao longo do tempo. Pessoas mais jovens, do sexo feminino, fumadoras, com pior percepção do estado de saúde ou com comorbidades apresentaram maior probabilidade de relatar não adesão medicamentosa relacionada a custos. Diversos fatores socioeconômicos também estavam associados a uma maior probabilidade de não adesão medicamentosa relacionada a custos: residir nas regiões do Centro-Oeste, Sul ou Oeste (em comparação com o Nordeste), não ter seguro de saúde, possuir um nível educacional mais baixo e ter uma renda familiar inferior a 400% do nível de pobreza federal.

Adultos com asma que relataram não adesão medicamentosa relacionada a custos tiveram maior probabilidade de sofrer exacerbações de asma (OR ajustado [aOR]=1,95; IC 95% 1,78–2,13) e visitas ao serviço de urgência devido à asma (aOR=1,63; IC 95% 1,44–1,84).

A tendência decrescente observada na prevalência da não adesão medicamentosa relacionada a custos entre 2011 e 2022 pode ser atribuída à implementação gradual do Affordable Care Act (ACA) desde 2010 e à expansão do Medicaid desde 2014, que ajudaram a tornar os cuidados de saúde mais acessíveis e econômicos para os americanos.⁹ A maior probabilidade de não adesão medicamentosa relacionada a custos entre pessoas com comorbidades também é digna de nota. Este achado, assim como os relacionados a outros fatores associados à não adesão medicamentosa, alinha-se a estudos sobre a mesma questão em outras condições crônicas.^{5,7} Evidências demonstram que pessoas com múltiplas condições têm maior probabilidade e frequência de utilizar os serviços de saúde,¹⁰ além de enfrentarem um maior fardo de medicação e tratamento,¹⁰ com os elevados custos associados contribuindo para a diminuição da adesão medicamentosa.

Importante, o trabalho de Hung et al.⁸ destaca que o Sul dos Estados Unidos apresentou um maior fardo de pessoas com asma que experienciaram não adesão medicamentosa relacionada a custos, em comparação com outras regiões dos EUA. Especificamente, o Sul teve a maior prevalência de não adesão medicamentosa relacionada a custos ao longo do tempo, a menor percentagem média anual de declínio nesta não adesão e foi uma das duas

regiões com maior probabilidade de ocorrer este tipo de não adesão (aOR Sul vs Nordeste=1,42, IC 95% 1,25–1,61; aOR Centro-Oeste vs Nordeste=1,42, IC 95% 1,26–1,60).

Estes resultados devem ser contextualizados à luz da história e do presente. O legado de racismo e desigualdade incorporado nas políticas de saúde, trabalho e sindicalização no Sul contribuiu para uma maior proporção de pessoas sem seguro de saúde e enfrentando barreiras financeiras para terem acesso aos cuidados de saúde.¹¹ Desde o início da expansão do Medicaid pelo Affordable Care Act (ACA) em 2014, quase 75% das pessoas de baixa renda e sem seguro de saúde residindo na chamada “lacuna de cobertura” (estados dos EUA que não adotaram a expansão) estão concentradas em três estados do Sul.¹²

A consideração da reforma contínua dos cuidados de saúde e medicamentos nos EUA também é crucial na interpretação dos resultados. Primeiramente, pesquisas futuras baseadas neste trabalho podem observar um padrão contínuo de declínio na não adesão medicamentosa relacionada a custos à medida que as reformas recentes são implementadas. O Inflation Reduction Act de 2022 introduziu limites nos gastos anuais do próprio bolso para inscritos no Medicare, facilitando, indiretamente, que empresas farmacêuticas reduzissem os custos dos medicamentos, incluindo os da asma, beneficiando uma ampla população dos EUA.¹³ Estas mudanças estão andamento podem contribuir para uma melhor adesão às prescrições de asma, aliviando parte do fardo financeiro dos cuidados de saúde.

Em segundo lugar, os autores mostram que pessoas que experienciam não adesão medicamentosa relacionada a custos têm maior probabilidade de sofrer exacerbações de asma.¹⁴ Dado que estes eventos são caros para o sistema de saúde dos EUA, os resultados reforçam a importância de esforços contínuos em políticas e legislação para reduzir as barreiras financeiras ao controle da asma.¹⁵

Apesar disso, o Programa de Negociação de Preços de Medicamentos do Medicare associado ao Inflation Reduction Act reduziu os custos de medicamentos para várias condições crônicas,¹⁶ mas ainda não incluiu medicamentos respiratórios, como os da asma, apesar do seu elevado custo bruto anual.^{4,17,18} Isso levanta a questão: certos medicamentos para asma deveriam ser incluídos na próxima negociação de preços?

Limitações do estudo de Hung et al.⁸ incluem os vieses comumente presentes no uso de dados de questionários: viés de recordação, classificação incorreta devido a autorrelatos e desafios em estabelecer temporalidade, típicos de estudos transversais. A classificação incorreta de DPOC como asma é uma possibilidade notável, especialmente entre pessoas idosas com asma que são fumadoras atuais ou ex-fumadoras.¹⁹ Embora a espirometria seja um componente essencial no diagnóstico diferencial,^{2,19} a ligação dos dados do NHIS aos dados clínicos não foi possível. Pesquisas futuras, baseando-se neste trabalho, podem considerar o uso do conjunto de dados do All of Us Research Program, onde os dados do

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NHIS poderiam ser analisados em conjunto com outras fontes de dados interligadas.²⁰

Em resumo, o estudo de Hung et al. sobre a não adesão medicamentosa relacionada a custos em pessoas com asma oferece informações valiosas para a nossa compreensão dessa questão em doenças crônicas. Os resultados destacam o papel substancial das políticas de saúde na redução do peso financeiro das prescrições para asma. Além disso, enfatizam que, ao considerar opções de tratamento para a asma, médico e doente devem focar numa abordagem personalizada, envolvendo discussões sobre as circunstâncias financeiras do doente.

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REFERÊNCIAS

- Centers for Disease Control and Prevention. Data, statistics, and surveillance: most recent national asthma data and archived most recent asthma data. 2023. Available: https://www.cdc.gov/asthma/most_recent_data.htm [Accessed 26 Oct 2024].
- Mosnaim G. Asthma in Adults. *N Engl J Med* 2023;389:1023–31.
- Yaghoubi M, Adibi A, Safari A, et al. The Projected Economic and Health Burden of Uncontrolled Asthma in the United States. *Am J Respir Crit Care Med* 2019;200:1102–12.
- Duan KI, Birger M, Au DH, et al. Health Care Spending on Respiratory Diseases in the United States, 1996–2016. *Am J Respir Crit Care Med* 2023;207:183–92.
- Khera R, Valero-Elizondo J, Das SR, et al. Cost-Related Medication Nonadherence in Adults With Atherosclerotic Cardiovascular Disease in the United States, 2013 to 2017. *Circulation* 2019;140:2067–75.
- Lago-Hernandez C, Nguyen NH, Khera R, et al. Cost-Related Nonadherence to Medications Among US Adults With Chronic Liver Diseases. *Mayo Clin Proc* 2021;96:2639–50.
- Wen X, Qiu H, Yu B, et al. Cost-related medication nonadherence in adults with COPD in the United States 2013–2020. *BMC Public Health* 2024;24:864.
- Hung C-T, Erickson SR, Wu C-H, et al. Cost-related non-adherence to medications among adults with asthma in the USA, 2011–2022. *Thorax* 2024.
- Kennedy J, Wood EG. Medication Costs and Adherence of Treatment Before and After the Affordable Care Act: 1999–2015. *Am J Public Health* 2016;106:1804–7.

- Skou ST, Mair FS, Fortin M, et al. Multimorbidity. *Nat Rev Dis Primers* 2022;8:48.
- Yearby R, Clark B, Figueroa JF. Structural Racism In Historical And Modern US Health Care Policy. *Health Aff (Millwood)* 2022;41:187–94.
- Drake P, Tolbert J, Rudowitz R, et al. How many uninsured are in the coverage gap and how many could be eligible if all states adopted the Medicaid expansion? KFF, 2024. Available: <https://www.kff.org/medicaid/issue-brief/how-many-uninsured-are-in-the-coverage-gap-and-how-many-could-be-eligible-if-all-states-adopted-the-medicaid-expansion/> [Accessed 26 Oct 2024].
- NBC News. Some drugmakers to cap cost of asthma inhalers at \$35 a month. NBC News; 2024. Available: <https://www.nbcnews.com/health/health-news/drugmakers-cap-cost-asthma-inhalers-35-monthly-na154536> [Accessed 26 Oct 2024].
- Mein SA, Tale A, Rice MB, et al. Out-of-Pocket Prescription Drug Savings for Medicare Beneficiaries with Asthma and COPD Under the Inflation Reduction Act. *J Gen Intern Med* 2024.
- Patel MR, Press VG, Gerald LB, et al. Improving the Affordability of Prescription Medications for People with Chronic Respiratory Disease. *Am J Respir Crit Care Med* 2018;198:1367–74.
- Centers for Medicare & Medicaid Services. Medicare Drug Price Negotiation Program: negotiated prices for initial price applicability year. 2026. Available: <https://www.cms.gov/newsroom/fact-sheets/medicare-drug-pricenegotiation-program-negotiated-prices-initial-price-applicability-year-2026> [Accessed 26 Oct 2024].
- Centers for Medicare & Medicaid Services. Dataset: Medicare Part B spending by drug [sorted by highest gross annual spending]. 2024. Available: <https://data.cms.gov/summarystatistics-on-use-and-payments/medicaremedicaid-spending-by-drug/medicare-part-b-spending-by-drug> [Accessed 26 Oct 2024].
- Centers for Medicare & Medicaid Services. Dataset: Medicare Part D spending by drug [sorted by highest gross annual spending]. 2024. Available: <https://data.cms.gov/summarystatistics-on-use-and-payments/medicaremedicaid-spending-by-drug/medicare-part-d-spending-by-drug> [Accessed Oct 2024].
- Nissen F, Morales DR, Mullerova H, et al. Concomitant diagnosis of asthma and COPD: a quantitative study in UK primary care. *Br J Gen Pract* 2018;68:e775–82.
- All of Us Research Program. Health care access and utilization: follow up survey details and resources. 2022. Available: <https://support.researchallofus.org/hc/en-us/articles/6085927411732-Health-Care-Access-and-Utilization-Follow-Up-Survey-Details-and-Resources> [Accessed 26 Oct 2024].

Os corticosteroides inalados (ICS) reduzem o risco de desfechos cardiovasculares em doentes com Doença Pulmonar Obstrutiva Crónica (DPOC)?

David M Mannino^{1,2}

A polimorbilidade é um componente importante da Doença Pulmonar Obstrutiva Crónica (DPOC), sendo as doenças cardiovasculares algumas das comorbilidades mais relevantes. O desenvolvimento de eventos cardiovasculares incidentes e recorrentes está relacionado ao grau de comprometimento da função pulmonar na DPOC. As exacerbações agudas da DPOC (AECOPD) estão associadas a um maior risco de desenvolvimento de eventos cardiovasculares agudos, especialmente nos primeiros 6 meses após a exacerbação. As terapias que incluem corticosteroides inalados (ICS) reduzem o risco de exacerbações. Assim, seria esperado que terapias que diminuam exacerbações, como as que incluem ICS, também reduzissem os eventos cardiovasculares.

Esse foi o tema do estudo "Study to Understand Mortality and Morbidity in COPD", um ensaio clínico de 3 anos com mais de 16 000 doentes randomizados em quatro grupos (placebo, furoato de fluticasona, vilanterol e fluticasona/vilanterol). Os grupos que incluíram ICS tiveram menos exacerbações e menor declínio da função pulmonar, mas não apresentaram reduções significativas na mortalidade ou em eventos cardiovasculares.

Os eventos cardiopulmonares são o foco do estudo em andamento "THARROS", um ensaio multicêntrico, randomizado, duplo-cego (Fase III), que avalia a eficácia do inalador de dose medida de budesonida, glicopirrónio e formoterol fumarato em comparação com glicopirrónio e formoterol fumarato em desfechos cardiopulmonares na DPOC. O estudo pretende recrutar até 5000 doentes, com conclusão estimada para 2028. O principal desfecho será o primeiro evento cardíaco grave ou evento associado à DPOC, comparando terapias triplas com broncodilatadores duplos.

O uso de ICS e seu efeito sobre os desfechos cardiovasculares também foi explorado por Ioannides et al. na edição original da Thorax. Os autores conduziram um estudo de coorte histórico com doentes com DPOC na Inglaterra, utilizando dados do Clinical Practice Research Datalink Aurum, associados a estatísticas hospitalares e de mortalidade do Office of National Statistics, cobrindo o período de 1 de janeiro de 2010 a 31 de dezembro de 2019. Eles não encontraram evidências de que o uso de ICS protegesse contra eventos cardiovasculares

adversos maiores (MACEs), embora tenham identificado indícios de proteção contra insuficiência cardíaca. Este artigo destaca tanto os benefícios quanto as limitações associadas às análises baseadas em "evidências do mundo real" (RWE).

Um dos principais benefícios é que estas coortes podem ser acompanhadas por períodos muito mais longos do que os doentes em ensaios clínicos. A média de seguimento nesta análise foi de 4,67 anos (desvio padrão de 3,29 anos), em contraste com ensaios clínicos randomizados (RCTs) nesta área, que geralmente apresentam seguimento de 1 a 4 anos, sendo os estudos mais recentes de apenas 1 ano. Os estudos baseados em evidências do mundo real (RWE) têm a capacidade de incluir um grupo mais abrangente de doentes do que os RCTs. Por exemplo, no estudo de Ioannides et al, mais de 77% das pessoas com DPOC que utilizavam ICS ou broncodilatadores foram incluídas nas análises. Em comparação, uma análise recente mostrou que, em média, apenas 11,2% dos doentes com DPOC em ambientes de prática geral atenderiam aos critérios de inclusão em RCTs.

No entanto, estudos RWE apresentam limitações importantes. A maior delas, reconhecida pelos autores, é que o tratamento não ocorre de forma aleatória. Os médicos têm razões específicas para escolher a terapia que prescrevem ao doente. Evidências deste fenómeno podem ser observadas nesta coorte; por exemplo, doentes em ICS tinham maior probabilidade de ter asma (46,9% vs 12,8%) e de terem sofrido uma exacerbação (37,5% vs 30%) em comparação com doentes que não usavam ICS. Curiosamente, 34,1% estavam em monoterapia com ICS, sugerindo um componente significativo de asma. Outra limitação importante, também reconhecida, é que a terapia foi avaliada apenas no início do tratamento, permitindo que os doentes mudassem de terapia (por exemplo, de ICS para não ICS, ou vice-versa), mas ainda fossem classificados com base no grupo inicial ao longo de todo o estudo. Em análises RWE, a troca de medicação ocorre frequentemente, sendo uma das mudanças mais comuns após uma exacerbação a evolução para terapias triplas (de terapia sem ICS para terapia com ICS).

Assim, doentes que não utilizavam ICS no início do estudo podem ter começado a usá-los nos anos posteriores devido a uma exacerbação. Na análise de Ioannides, o efeito da exposição ao ICS sobre insuficiência cardíaca e mortalidade cardiovascular mostrou-se protetor nos primeiros anos do estudo (quando o grupo com ICS provavelmente estava de fato em terapia,

enquanto o grupo sem ICS não estava), mas não nos anos posteriores do estudo (quando é possível que o grupo inicialmente sem ICS tenha começado a usar ICS após uma exacerbação). Este tipo de viés de classificação incorreta, para terapias que podem mudar, aumenta com a maior duração do estudo.

A relação entre exacerbações agudas e eventos cardiovasculares foi investigada considerando diversos mecanismos possíveis, como desajuste ventilação/perfusão, inflamação sistêmica, stresse oxidativo, estado de hipercoagulabilidade, hipertensão pulmonar e hiperinsuflação dinâmica. Há também a hipótese de que o tratamento das exacerbações, que inclui atualmente esteroides sistêmicos e broncodilatadores, pode contribuir para efeitos como retenção de líquidos, taquiarritmias e eventos cardiovasculares. Essa questão ainda precisa de uma avaliação mais específica para determinar se uma maior exposição a estes agentes aumenta o risco de eventos cardiovasculares adversos maiores (MACEs).

No curto prazo, é plausível afirmar que existe uma relação entre ICS e redução de MACEs. A capacidade dos corticosteroides inalados (ICS) de reduzir exacerbações tem sido consistentemente demonstrada em diversos estudos realizados em várias populações. Tanto as exacerbações moderadas quanto as graves estão claramente associadas a um aumento no risco de MACEs. No entanto, a análise de Ioannides et al levanta dúvidas se este benefício é mantido a longo prazo, com a resposta a essa questão, em um horizonte temporal maior, sendo incerta. Não existem ensaios clínicos randomizados (RCTs) que tenham investigado estas terapias por mais de quatro anos.

Com o surgimento de novas terapias aprovadas para a DPOC, que não incluem corticosteroides inalados ou broncodilatadores de longa duração, a avaliação dessas terapias poderá fornecer dados adicionais importantes para abordar esta questão.

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REFERÊNCIAS

1 Martinez CH, Mannino DM, Divo MJ. Defining COPD-Related Comorbidities, 2004-2014. *Chronic Obstr Pulm Dis* 2014;1:51–63.

2 Johnston AK, Mannino DM, Hagan GW, et al. Relationship between lung function impairment and incidence or recurrence of cardiovascular events in a middle-aged cohort. *Thorax* 2008;63:599–605.

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- 3 Daniels K, Lanes S, Tave A, et al. Risk of Death and Cardiovascular Events Following an Exacerbation of COPD: The EXACOS-CV US Study. *Int J Chron Obstruct Pulmon Dis* 2024;19:225–41.
- 4 Whittaker H, Nordon C, Rubino A, et al. Frequency and severity of respiratory infections prior to COPD diagnosis and risk of subsequent postdiagnosis COPD exacerbations and mortality: EXACOS-UK health care data study. *Thorax* 2023;78:760–6.
- 5 Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med* 2018;378:1671–80.
- 6 Rabe KF, Martinez FJ, Ferguson GT, et al. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *N Engl J Med* 2020;383:35–48.
- 7 Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016;387:1817–26.
- 8 AstraZeneca. A study evaluating the efficacy of budesonide, glycopyrronium and formoterol fumarate metered dosed inhaler on cardiopulmonary outcomes in chronic obstructive pulmonary disease (THARROS). 2024. Available: <https://clinicaltrials.gov/study/NCT06283966> [Accessed 22 Oct 2024].
- 9 Ioannides AE, Kallis C, Whittaker HR, et al. Inhaled corticosteroids and major cardiovascular events in people with chronic obstructive pulmonary disease. *Thorax* 2024.
- 10 Calverley PMA, Anderson JA, Brook RD, et al. Fluticasone Furoate, Vilanterol, and Lung Function Decline in Patients with Moderate Chronic Obstructive Pulmonary Disease and Heightened Cardiovascular Risk. *Am J Respir Crit Care Med* 2018;197:47–55.
- 11 Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543–54.
- 12 Whittaker HR, Torkpour A, Quint J. Eligibility of patients with chronic obstructive pulmonary disease for inclusion in randomised control trials investigating triple therapy: a study using routinely collected data. *Respir Res* 2024;25:43.
- 13 Bogart M, Germain G, Laliberté F, et al. Real-World Treatment Patterns and Switching Following Moderate/ Severe Chronic Obstructive Pulmonary Disease Exacerbation in Patients with Commercial or Medicare Insurance in the United States. *Int J Chron Obstruct Pulmon Dis* 2023;18:1575–86.
- 14 Simons SO, Heptinstall AB, Marjens Z, et al. Temporal Dynamics of Cardiovascular Risk in Patients with Chronic Obstructive Pulmonary Disease During Stable Disease and Exacerbations: Review of the Mechanisms and Implications. *Int J Chron Obstruct Pulmon Dis* 2024;19:2259–71.
- 15 Gershon A, Croxford R, Calzavara A, et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. *JAMA Intern Med* 2013;173:1175–85.
- 16 Pujades-Rodriguez M, Morgan AW, Cubbon RM, et al. Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: A population-based cohort study. *PLoS Med* 2020;17:e1003432.
- 17 McCormick B. FDA approves dupilumab as first biologic treatment for COPD. 2024. Available: <https://www.ajmc.com/view/fda-approves-dupilumab-as-first-biologic-treatment-for-copd> [Accessed 26 Oct 2024].
- 18 McCormick B. FDA approves ensifentrine for maintenance treatment of adult patients with COPD. 2024. Available: <https://www.ajmc.com/view/fdaapproves-ensifentrine-for-maintenance-treatment-of-adult-patients-with-copd> [Accessed 26 Oct 2024].

A relevância clínica dos serotipos capsulares na pneumonia por *Streptococcus pneumoniae*

Jeremy Stuart Brown

As infecções do trato respiratório inferior (LRTIs) continuam a ser uma das principais causas de mortalidade respiratória, sendo responsáveis, anualmente, por aproximadamente 40.000 mortes no Reino Unido e 2,7 milhões a nível global. A pneumonia adquirida na comunidade (CAP) é a LRTI mais grave no Reino Unido, com uma taxa de mortalidade de 8% entre os doentes hospitalizados. A sua incidência tem aumentado à medida que a população envelhece. Apesar de *Streptococcus pneumoniae* ser a única causa bacteriana comum de LRTIs para a qual existe uma vacina eficaz, esta bactéria continua a ser a principal causa bacteriana de LRTIs, sendo responsável por 16% dos casos fatais globalmente e por 40% das CAP hospitalizadas no Reino Unido.

O estudo publicado por Lansbury et al. nesta edição da *Thorax* com artigos do *Archives Disease in Childhood*, apresenta dados adicionais que sublinham os desafios em reduzir a elevada morbimortalidade causada por *S. pneumoniae*. Lansbury et al. analisaram dados de 5186 pacientes com CAP admitidos em dois hospitais de Nottingham entre 2013 e 2023, dos quais 2193 (42%) foram causados por *S. pneumoniae*. Este estudo destaca-se por diversas razões: (1) o tamanho da amostra e a duração permitem avaliar mudanças ao longo do tempo; (2) foi realizado em locais com ampla experiência em investigação de CAP; e (3) utilizou o teste de antígeno urinário Bioplex-24 para diagnosticar CAP por *S. pneumoniae* e identificar o serotipo capsular causador.

S. pneumoniae é envolvido por uma cápsula constituída por cadeias repetidas de três ou quatro unidades de monossacarídeos, com composições químicas variadas que resultam em mais de 100 serotipos capsulares diferentes. Todas as vacinas existentes para *S. pneumoniae* baseiam-se em antígenos capsulares e protegem apenas contra os serotipos incluídos na vacina; portanto, os serotipos predominantes na CAP são cruciais para a eficácia vacinal. O teste Bioplex-24 identifica a presença de antígenos capsulares de 24 serotipos comuns causadores de doenças em amostras de urina, e um resultado positivo sugere infecção com aquele serotipo específico de *S. pneumoniae*. A concordância entre os resultados do Bioplex-24 e os dados de cultura sanguínea sobre o serotipo infetante é de 80%, sendo os restantes 20% divididos entre serotipos discordantes, infecções com serotipos não identificados pelo Bioplex-24, ou resultados negativos no teste.

Embora ainda não se saiba com que frequência a colonização nasofaríngea por *S. pneumoniae* sem pneumonia possa gerar um resultado positivo no teste Bioplex-24, a baixa carga bacteriana durante a colonização e a elevada concordância com os resultados de cultura sanguínea sugerem

fortemente que um teste positivo no Bioplex-24 em um doente com CAP reflete o agente patogénico causador. Apesar de não identificar infecções por serotipos não incluídos no teste, o Bioplex-24 duplicou a proporção de casos de CAP atribuídos a *S. pneumoniae*, podendo assim melhorar significativamente a atual taxa insatisfatória de identificação do agente patogénico causador em pacientes com CAP.

Lansbury et al. mostram que a proporção de pneumonia adquirida na comunidade (CAP) causada por *Streptococcus pneumoniae* aumentou de 36% em 2013 para 67% em 2023, um aumento surpreendentemente grande e difícil de explicar completamente. Uma análise mais detalhada dos dados indica que, antes da pandemia de COVID-19, a proporção de CAP causada por *S. pneumoniae* aumentava gradualmente, passando de um mínimo de 32% em 2015–2016 para 44% em 2018–2019, mas um aumento significativo adicional ocorreu durante a pandemia.

As razões subjacentes a esta mudança não são totalmente claras. Parte do aumento pode refletir uma maior proporção de CAP atribuída a *S. pneumoniae* com o envelhecimento da população. No entanto, o aumento parece ser impulsionado principalmente por uma queda inesperada nos casos de CAP não pneumocócica ao longo do tempo. A supressão da prevalência de vírus respiratórios durante os confinamentos pode ter contribuído para a redução de CAP não pneumocócica, mas a proporção aumentada de CAP pneumocócica continuou mesmo após a pandemia, quando a incidência de infecções respiratórias virais voltou a subir.

Além disso, o critério de admissão para pacientes com CAP pode ter mudado ao longo do tempo, excluindo casos menos graves de CAP. Como a CAP causada por *S. pneumoniae* está associada a pontuações CURB65 mais elevadas e maiores taxas de internamento em cuidados intensivos, essa mudança pode ter reduzido a prevalência relativa de CAP não pneumocócica. Outro fator pode ser que a CAP não pneumocócica tende a desenvolver-se de forma mais lenta do que a CAP por *S. pneumoniae*. O aumento das consultas remotas e da prescrição de antibióticos pode ter reduzido desproporcionalmente as admissões de casos menos graves, como CAP não pneumocócica.

Independentemente das razões subjacentes a este aumento na proporção de admissões por CAP atribuídas a *S. pneumoniae*, essa mudança reforça a necessidade de uma política vacinal mais eficaz contra *S. pneumoniae* para adultos.

Como a CAP causada pelo serotipo 3 não resulta em casos mais graves do que os causados por outros serotipos, a alta prevalência do serotipo 3 não apresenta implicações significativas para a gestão clínica. No entanto, possui importantes implicações potenciais para as políticas de vacinação. Os adultos são vacinados com a vacina pneumocócica polissacarídica (PPV), que protege contra 23 serotipos (incluindo o serotipo 3), mas

apresenta uma eficácia relativamente baixa na prevenção da pneumonia, especialmente em indivíduos com mais de 75 anos.

A baixa eficácia da PPV tem estimulado um interesse recente na vacinação de adultos com novas vacinas conjugadas pneumocócicas (PCVs) que abrangem um leque mais amplo de serotipos, como PCV15, 20 e 21. Estas, teoricamente, poderiam proteger contra mais de 80% dos serotipos causadores de CAP. Contudo, a eficácia limitada das vacinas pneumocócicas contra o serotipo 3 compromete a rentabilidade geral das estratégias de vacinação, mesmo se as políticas forem ajustadas para incluir as novas PCVs de maior valência.

Em conclusão, Lansbury et al. demonstram uma carga contínua e cada vez mais elevada de CAP causada por *S. pneumoniae* em adultos, o que reforça a necessidade de políticas de vacinação eficazes (incluindo, potencialmente, as novas PCVs de maior valência). No entanto, o fato de as estirpes do serotipo 3 serem a causa dominante complica a elaboração destas políticas devido à sua relativa resistência à prevenção por vacinação.

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REFERÊNCIAS

- 1 GBD 2015 LRI Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis* 2017;17:1133–61.
- 2 Lansbury L, Lawrence H, McKeever TM, et al. Pneumococcal serotypes and risk factors in adult community-acquired pneumonia 2018–20; a multi-centre UK cohort study. *Lancet Reg Health Eur* 2024;37:100812.
- 3 Millett ER, Quint JK, Smeeth L, et al. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. *PLoS ONE* 2013;8:e75131.
- 4 IHME Pathogen Core Group. Global burden associated with 85 pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Infect Dis* 2024;24:868–95.
- 5 Lansbury L, McKeever TM, Lawrence H, et al. Pneumococcal pneumonia trends in adults hospitalised with community-acquired pneumonia over 10 years (2013–2023) and the role of serotype 3. *Thorax* 2025;80:86–96.
- 6 Vestesson E, De Corte K, Chappell P, et al. Antibiotic prescribing in remote versus face-to-face consultations for acute respiratory infections in primary care in England: an observational study using target maximum likelihood estimation. *EClinMed* 2023;4:102245.
- 7 Hyams C, Lahuerta M, Theilacker C, et al. Surveillance of pneumococcal serotypes in adults hospitalised with acute lower respiratory tract infection in Bristol, UK. *Vaccine* 2024;42:1599–607.
- 8 Grant LR, Begier E, Theilacker C, et al. Multicountry Review of Streptococcus pneumoniae Serotype Distribution Among Adults With Community-Acquired Pneumonia. *J Infect Dis* 2024;229:282–93.
- 9 Andrews N, Kent A, Amin-Chowdhury Z, et al. Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: The indirect cohort design, 2006–2018. *Vaccine* 2019;37:4491–8.
- 10 Bertran M, D'Aeth JC, Abdullahi F, et al. Invasive pneumococcal disease 3 years after introduction of a reduced 1 + 1 infant 13-valent pneumococcal conjugate vaccine immunisation schedule in England: a prospective national observational surveillance study. *Lancet Infect Dis* 2024;24:546–56.
- 11 Berild JD, Winje BA, Vestheim DF, et al. A Systematic Review of Studies Published between 2016 and 2019 on the Effectiveness and Efficacy of Pneumococcal Vaccination on Pneumonia and Invasive Pneumococcal Disease in an Elderly Population. *Pathogens* 2020;9:259.
- 12 Lawrence H, Pick H, Baskaran V, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against vaccine serotype pneumococcal pneumonia in adults: A case-control test-negative design study. *PLoS Med* 2020;17:e1003326.

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Hora de abordar a questão: desclassificar alergias à penicilina e outros beta-lactâmicos em crianças e jovens

Paul Turner^{1,2}

Um em cada 10 crianças é rotulado como 'alérgico à penicilina', a maioria antes de iniciar a escola.¹ Na maioria dos casos, trata-se de exantema viral incorretamente classificado como 'alergia'. Confirmar uma alergia verdadeira é ainda mais complicado, já que cerca de 80% das crianças pequenas com alergia verdadeira à penicilina superam essa alergia em 10 anos.² Como resultado, cerca de 95% dos rótulos de alergia à penicilina são considerados incorretos em investigações formais.³

A British Society for Allergy and Clinical Immunology (BSACI) publicou uma diretriz em 2022 para ajudar os clínicos do Reino Unido (sem formação formal em alergologia) a desenvolver um serviço de desclassificação de alergias à penicilina para os seus doentes.³ Essa diretriz baseia-se em mais de 10 anos de evidências que mostram que o "teste de provocação oral" direto ou o teste de provocação medicamentosa (DPT) sem avaliação inicial por um especialista é seguro.⁴

A desclassificação de alergias à penicilina precisa de ser uma prioridade para os pediatras do Reino Unido.⁵ O National Institute for Health and Care Excellence recomenda que os clínicos "verifiquem novamente" doentes rotulados como "alérgicos à penicilina" antes de prescrever um antibiótico não penicilínico, como estratégia essencial para reduzir a resistência antimicrobiana ao nível populacional.⁶ Ainda assim, um inquérito publicado no ano passado revelou que menos de metade dos pediatras do Reino Unido questionariam sequer um rótulo de "alergia à penicilina".⁶

Foram publicados três artigos que aprofundam a base de evidências para apoiar a desclassificação de alergias à penicilina. Wilkins et al. relataram uma série retrospectiva de 1259 testes orais de DPT com um beta-lactâmico (tipicamente amoxicilina).⁷ No total, 80 (6,4%) dos testes foram considerados positivos: 18 (1,4%) na dose inicial administrada no hospital e 62 (4,9%) em casa (os pacientes receberam um curso de 5 dias do antibiótico após o DPT inicial no hospital).

Dois casos de anafilaxia foram relatados com a dose inicial administrada no hospital, embora um terceiro caso também devesse ser considerado como anafilaxia devido aos sintomas relatados (tosse transitória, rouquidão vocal e sibilância). Preditores de um DPT "reativo" (indicando uma alergia verdadeira em curso) incluíam um histórico de outras alergias a medicamentos e uma reação inicial considerada "imediate"



Figura 1: De cada 100 crianças que relatam alergia à penicilina ou amoxicilina, apenas uma estará em risco de uma reação alérgica do tipo imediato (que pode causar anafilaxia). Quatro apresentarão erupções cutâneas retardadas, que podem ou não ser alérgicas, enquanto 95% não terão qualquer reação.

(início <1 hora após a dose) e "grave". Cerca de 4% dos testes foram considerados equivocados, mas, no geral, quase 90% das crianças foram desclassificadas.

Grewal e Jay contactaram 313 crianças e jovens com histórico de alergia a antibióticos, sendo 87% destas reações relacionadas com beta-lactâmicos, que haviam frequentado o serviço de urgências.⁸ Conseguiram contactar 200 (64%) destas crianças, que foram estratificadas por risco com base num questionário. Quinze delas foram diretamente desclassificadas com base no histórico clínico, enquanto as restantes 185 receberam a opção de realizar o teste de provocação medicamentosa (DPT), que incluía uma dose inicial supervisionada seguida por um curso de 4 dias de antibiótico administrado em casa. Quando a reação inicial era leve e com início retardado, a dose inicial do DPT foi administrada em contexto de consulta de medicina geral, em vez de um ambiente hospitalar. No total, 138 crianças realizaram o teste de provocação, das quais 20 em cuidados primários, sem quaisquer

reações imediatas. No entanto, nove crianças (6,4%) apresentaram reações leves e de início retardado. O processo foi considerado aceitável, com base no feedback positivo dos doentes e numa taxa elevada de resposta, já que 75% das famílias concordaram em participar no teste. Ao final, 142 das 313 crianças (45%) foram desclassificadas com sucesso.

No Reino Unido, a desclassificação de alergias a antibióticos é, geralmente, realizada quando as crianças estão saudáveis.³ No entanto, Wong et al adotaram uma abordagem diferente, recrutando crianças que frequentavam a unidade de avaliação urgente devido a doença.⁹ Observou-se que 65% das reações relacionadas estavam relacionadas com beta-lactâmicos e, com a aplicação de uma ferramenta de estratificação de risco, 37 de 80 crianças (46%) foram desclassificadas com sucesso no cenário agudo. Estes estudos mostram que estratégias proativas para desclassificar crianças com alergia a antibióticos são seguras, podem ser realizadas em contextos não especializados e alcançam uma taxa de sucesso de cerca de 50%.

Dois pontos continuam a gerar dúvidas. O primeiro está relacionado à necessidade de avaliação especializada em crianças cuja reação inicial tem início imediato, ou seja, em menos de 1 hora após a dose, mas que não seja grave, como urticária isolada ou uma erupção cutânea leve. A maioria dos algoritmos, incluindo os da BSACI, sugere que reações imediatas devem ser critério para avaliação por um especialista.³ Grewal e Jay, por outro lado, incluíam crianças com este histórico em desafios realizados em ambulatório, mas com o suporte de uma equipa de alergologia pediátrica. O segundo ponto prende-se com o curso de 3 a 5 dias do antibiótico a ser tomado em casa após o DPT inicial, para excluir reações de hipersensibilidade retardadas.³ A base de evidências para esta etapa ainda é limitada,^{1,11} embora estudos, como o de Wilkins et al, demonstrem que um DPT¹⁰ prolongado pode identificar crianças com reações de início retardado.⁷ Por este motivo, muitas diretrizes continuam a incluir esta etapa como parte do protocolo.³

Um algoritmo proposto para a desclassificação de alergias a antibióticos em crianças e jovens, tanto em ambiente hospitalar como em cuidados primários supervisionados, é apresentado na Figura 2. A desclassificação de alergias a antibióticos em crianças é uma prática segura, económica e, acima de tudo, uma boa prática clínica. Já é hora de tornar esta abordagem uma

Table 1 Features proposed considered to indicate a higher likelihood of allergic reaction to a beta-lactam⁹

Clinical feature	
'Severe features' =More likely	▶ Anaphylaxis ▶ Respiratory compromise (including acute wheeze) ▶ Angio-oedema ▶ Extensive urticaria ▶ Arrhythmia or cardiovascular collapse or hypotension or shock ▶ Severe cutaneous adverse reactions including exfoliation/desquamation ▶ Mucosal involvement ▶ Serum sickness-like reaction ▶ Cytopenia ▶ Organ involvement (eg, acute interstitial nephritis, DRESS syndrome)
Less likely	▶ Isolated urticaria or mild rash ▶ Persistent gastrointestinal features (including vomiting and cramps) ▶ Itching ▶ Isolated exanthem (maculopapular eruption)

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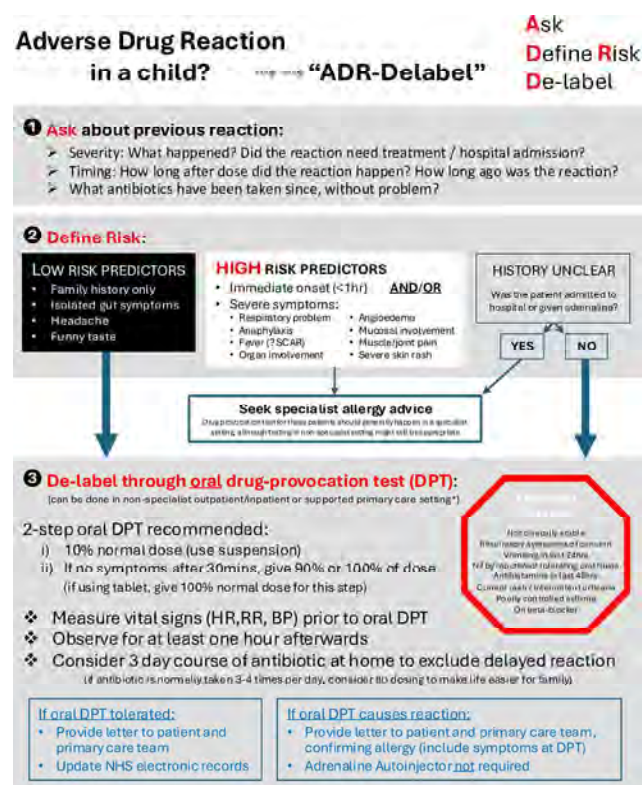


Figura 2: apresenta um algoritmo que auxilia na desclassificação de alergias à penicilina e outros beta-lactâmicos em crianças e jovens em contextos não especializados. Um ambiente de cuidados primários apoiados refere-se a um local onde o uso de anafilaxias não representa dificuldades em termos de equipa, tratamento ou monitorização. Quando o teste de provocação medicamentosa oral (DPT) é realizado neste contexto, é necessário que um profissional pediátrico sénior esteja informado e disponível (pelo menos por telefone) em tempo real para orientação. Se existirem critérios de exclusão, o DPT oral deve ser adiado e/ou deve-se procurar aconselhamento especializado em alergologia. BP: pressão arterial, DPT: teste de provocação medicamentosa, HR: frequência cardíaca, NHS: Serviço Nacional de Saúde (National Health Service), RR: frequência respiratória, SCAR: reação adversa cutânea grave.

rotina e um componente integral da formação pediátrica.

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REFERÊNCIAS

- Vyles D, Adams J, Chiu A, et al. Allergy Testing in Children With Low-Risk Penicillin Allergy Symptoms. *Pediatrics* 2017;140:e20170471.
- Romano A, Gaeta F, Valluzzi RL, et al. Natural evolution of skin-test sensitivity in patients with IgE-mediated hypersensitivity to cephalosporins. *Allergy* 2014;69:806–9.
- Savic L, Arden-Jones M, Avery A, et al. BSACI guideline for the set-up of penicillin allergy de-labelling services by non-allergists working in a hospital setting. *Clin Exp Allergy* 2022;52:1135–41.
- Srisuwatchari W, Phinyo P, Chiriac AM, et al. The Safety of the Direct Drug Provocation Test in Beta-Lactam Hypersensitivity in Children: A Systematic Review and Meta-Analysis. *J Allergy Clin Immunol Pract* 2023;11:506–18.
- Turner P. Delabelling penicillin allergy is not rocket science. *Arch Dis Child* 2023;108:329.
- Madueme K, Clark H, Sohal I, et al. Paediatric Research Across the Midlands (PRAM) Network. Barriers to paediatric penicillin allergy de-labelling in UK secondary care: a regional survey. *Arch Dis Child* 2023;108:363–6.
- Wilkins AL, Pittet LF, Kyriakou S, et al. Allergy to beta-lactam antibiotics in children: predictors for a positive oral challenge test. *Arch Dis Child* 2025;110:31–7.
- Grewal A, Jay N. Outpatient and primary care direct provocation challenges for antibiotic allergy in children. *Arch Dis Child* 2025;110:23–5.
- Wong J, Atkinson A, Timberlake K, et al. Improving inpatient paediatric de-labelling of allergies to beta-lactams: a quality improvement study. *Arch Dis Child* 2025;110:26–30.
- Sáenz de Santa María R, Bogas G, Labella M, et al. Approach for de-labelling beta-lactam allergy in children. *Front Allergy* 2023;4:1298335.
- Exius R, Gabrielli S, Abrams EM, et al. Establishing Amoxicillin Allergy in Children Through Direct Graded Oral Challenge (GOC): Evaluating Risk Factors for Positive Challenges, Safety, and Risk of Cross-Reactivity to Cephalosporins. *J Allergy Clin Immunol Pract* 2021;9:4060–6.

ARTIGO ORIGINAL

O suporte respiratório não invasivo (NRS) desempenha um papel crucial nos cuidados paliativos pediátricos, especialmente para crianças e jovens adultos com condições médicas complexas

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RESUMO

Objetivo: Investigar a dificuldade respiratória (dispneia) e os distúrbios respiratórios do sono (SDB), que são comuns em crianças com condições limitantes da vida, mas cujos tratamentos com ventilação não invasiva (NIV) ou pressão positiva contínua nas vias aéreas (CPAP) ainda são pouco estudados. O estudo descreveu o uso de NIV/CPAP a longo prazo em crianças num programa de cuidados paliativos pediátricos na França.

Métodos: Foi realizado um levantamento transversal com crianças e jovens adultos com condições médicas complexas tratados na rede francesa de NIV pediátrica com NIV/CPAP a longo prazo. Foram analisadas as características dos doentes, bem como os resultados relacionados aos benefícios percebidos do NIV/CPAP.

Resultados: Os dados de 50 doentes (68% meninos) com idade mediana de 12 anos (variação de 0,4 a 21 anos) foram analisados. Vinte e três doentes (46%) apresentavam distúrbios do sistema nervoso central e cinco (10%) tinham anomalias cromossômicas. Trinta e dois pacientes (64%) foram tratados com NIV e 18 (36%) com CPAP. O uso de NIV/CPAP foi iniciado devido a um índice de apneia-hipopneia anormal em 18 doentes (36%), trocas gasosas noturnas anormais em 28 (56%) e após falência respiratória aguda em 11 (22%) dos doentes. A adesão média ao uso de NIV/CPAP foi de 9,3±3,7 horas por noite. O tratamento esteve associado a uma redução da dispneia em 60% dos doentes, aumento da duração do sono em 60%, melhoria na qualidade do sono em 74% e melhoria no sono dos pais em 40%.

Conclusões: Em crianças com condições limitantes da vida, o uso prolongado de NIV/CPAP pode estar associado ao alívio da dispneia, à melhoria dos SDB e ao benefício secundário de melhorar o sono dos pais.

INTRODUCTION

The number of children with complex and life-limiting conditions and managed within a paediatric palliative care (PPC) programme is increasing. Indeed, due to improvement in care and innovative therapies, especially for rare and complex diseases, the number of children surviving with chronic disorders and multiple comorbidities is increasing. A study performed in 2018 during a 6-month period in a respiratory intermediate care unit of a tertiary paediatric university in Italy identified 130 children with medical complexity managed within a PPC programme.¹ One hundred and ten (85%) patients had a rare disease, 42 (33%) a neuromuscular disorder and 33 (25%) a central ner-

Key messages

What is known about this topic

- Dyspnoea and sleep-disordered breathing (SDB) are common in children with life-limiting conditions managed within a palliative care programme.
- Studies on treatment with non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP) in children in palliative care are scarce.
- Data on the subjective benefit of NIV or CPAP in children in palliative care are lacking.

What this study adds

- In children with life-limiting conditions, NIV or CPAP may be associated with a relief of dyspnoea.
- In children with life-limiting conditions, NIV or CPAP may be associated with an improvement in sleep duration and sleep quality.
- NIV or CPAP in children in palliative care may be associated with an improvement in their parents' sleep.

How this study might affect research practice or policy

- Children with life-limiting conditions should be screened for dyspnoea and SDB.
- SDB should be evaluated by minimally invasive tools in order to minimise burden on patients and families.
- The potential benefit of NIV or CPAP should be evaluated by experts in sleep and NIV.

vous system disorder. A national survey performed in Spain in 2019 identified 164 children managed within 14 PPC teams, with oncological, neurological or neuromuscular diseases being the most common diseases.²

PPC is a complex mosaic of activities that aim to relieve suffering and provide comfort to patients and their families, addressing their physical, psy-



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chological, spiritual, social and ethical needs. The International Standards for PPC were published in 2022 and state that the main goal is to prevent or eradicate distressing symptoms in order to optimise the quality of life of the child and his family.³ The child's physical symptoms should be assessed, treated and monitored according to the patient's individual response, age, culture, and whether care is performed at home or in a hospital or hospice.

Dyspnoea and sleep problems are among the most common symptoms reported by children with life-limiting conditions and have a major impact on the child's and family's quality of life.⁴ Among the 164 children managed by a PPC in Spain, dyspnoea was the most common symptom, reported by 63% of the patients, followed by pain (50%), excessive secretions (48%) and sleep problems (47%).² This high prevalence of dyspnoea and sleep problems contrasts with the lack of tools and guidelines to screen and treat these symptoms. An online questionnaire completed by 23 PPC experts from 13 countries on symptoms commonly encountered in PPC showed that 50% of the experts found it 'difficult' or 'very difficult' to find specific literature and evidence on managing sleep disorders.⁵ Sleep disorders were ranked among the top three difficult symptoms or problems, on the same level as delirium, dystonia and neuroirritability.⁵

The aim of non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP) is to correct or improve sleep-disordered breathing (SDB) and dyspnoea.^{6,7} However, the literature on the use of NIV/CPAP in PPC is scarce. Of the 130 children with complex disease managed by a respiratory team in Italy, 47 (36%) were treated with long-term NIV >12 hours/day and 26 (20%) with invasive ventilation. In the Spanish survey, 12% of the 164 patients were treated with NIV with the same number being treated with invasive ventilation. However, no information is available on the criteria that led to the initiation of NIV, the tolerance and adherence of the patients, and the benefit of NIV with regard to patient-related outcome measures (PROMs) such as quality of sleep and quality of life. As such, the benefit of NIV in children in PPC with regard to the improvement in dyspnoea, quality of sleep and quality of life was listed as one of the research priorities by the recent European Respiratory Society Statement on paediatric long-term non-invasive respiratory support.⁷

The aim of the study was to describe the characteristics of children and young adults with a life-limiting condition, treated with long-term NIV/CPAP in France between December 2022 and March 2023.

MATERIAL AND METHODS

The study was a national cross-sectional survey performed among the French national paediatric NIV network which gathers 28 paediatric university centres.⁸ From 1 December 2022 to 31 March 2023, the referring paediatrician of the centre filled in an anonymous questionnaire for every child treated since at least 3 months with NIV or CPAP within a PPC or equivalent. Only patients belonging to life-limiting or life-threatening conditions of Category 3 ('Progressive conditions without curative treatment options') or Category 4 ('Irreversible but non-progressive conditions causing severe disability leading to susceptibility to health complications and likelihood of premature death') were included.⁹ Patients with neuromuscular disease were excluded as they represent a specific disease entity belonging to Category 2 (Conditions where premature death is inevitable).⁹ As not every hospital has a specific PPC, patients were included if their care comprised at least two of the following multidisciplinary decisions:

- ▶ 'Limitation of care'
- ▶ 'Do-not-intubate' decision
- ▶ 'Comfort care only'
- ▶ Management by a PPC
- ▶ Management by a paediatric pain team
- ▶ Presence of an advanced directive.

Some young adults, aged 18–21 years, who were followed within the NIV paediatric network since childhood and initiated on NIV/CPAP before the age of 18 years, and who were not yet transitioned to an adult centre, were also included.

Table 1 Patient-related outcomes on the subjective benefit of non-invasive ventilation/continuous positive airway pressure (NIV/CPAP)

	Yes	No
Is NIV/CPAP associated with a decrease in dyspnoea in your child?		
Is NIV/CPAP associated with an improvement in sleep duration in your child?		
Is NIV/CPAP associated with an improvement in sleep quality in your child?		
Is NIV/CPAP associated with an improvement in your own sleep duration or quality?		
Optional open response(s)		

The survey was developed by the members of the NIV network and comprised the same information collected on a previous national survey on long-term paediatric NIV/CPAP such as age, gender, main diagnosis, investigations performed before NIV/CPAP initiation, parameters that led to the decision of NIV/CPAP treatment, NIV/CPAP duration, mean objective NIV/CPAP adherence during the last month obtained from the device built-in software, type of interface, NIV/CPAP settings and the prescription of additional respiratory technologies at home.⁸ Within the context of PPC, additional information on medical treatment and non-respi-

Table 2 Characteristics of the patients

Median (range) age, years	12 (0.4–21)
Male/female, n (%)	34 (68%)/16 (32%)
Diagnosis	
Central nervous system disorder	
Encephalopathy (unknown origin)	4
MeCP2 mutation	3
Cerebral malformation	2
Rett syndrome	2
Perinatal anoxia	2
Cerebral tumour	2
Lennox-Gastaut syndrome	2
Metachromatic leucodystrophy	1
Woxx deficiency	1
Kleefstra syndrome	1
Joubert syndrome	1
Ceroid lipofuscinosis	1
Sulphate oxidase deficiency	1
Chromosomal anomaly	
Pallister-Killian syndrome	1
Other chromosomal anomaly	4
Peripheral neurological disease	
Neuroaxonal dystrophy	1
Sensitivo-motor neuropathy	1
Congenital myasthenia with sequelae of cardiac arrest	1
Mitochondrial cytopathy	3
Mucopolysaccharidosis type II	3
Polymalformative syndrome	2
Fibrodysplasia ossificans progressiva	2
Mucopolipidosis type II	1
Kenny-Caffey syndrome	1
CHARGE syndrome	1
Prader-Willi syndrome	1
Down syndrome	1
Pulmonary atresia with pulmonary hypertension	1
Immune deficiency	1
Congenital methemoglobinemia	1
Heart-lung transplantation after rhabdoid tumour	1

Table 3 Palliative care decisions and chronic treatment

Palliative care decisions	
'Limitation of care'	49 (98%)
'Do-not-intubate' decision	36 (72%)
'Comfort care only'	23 (46%)
Management by a paediatric palliative care team	33 (66%)
Management by a paediatric pain team	25 (50%)
Advanced directive	35 (70%)
Drugs	
Opioids	18 (36%)
Analgesics	24 (48%)
Anxiolytics	15 (30%)
Melatonin	12 (22%)
Nutritional support	
Nasogastric tube	3 (6%)
Gastrostomy	34 (68%)
Respiratory equipment	
Home oxygen therapy	30 (60%)
Home pulse oximeter	31 (62%)
Suction equipment	31 (62%)
Airway clearance device	
Intermittent positive pressure breathing	7 (14%)
Mechanical insufflator-exsufflator	11 (22%)
Intrapulmonary percussive ventilation	7 (14%)

ratory technologies was also gathered. As every patient was seen at least every 3 months on a routine basis, PROMs about the subjective benefit of NIV/CPAP were asked by the referring paediatric pulmonologist to the parents and patients >6 years when possible (family/patient), during a routine follow-up visit (table 1). All responses were centralised and analysed by the NIV centre of Necker hospital. All the families/patients gave their informed consent.

RESULTS

The data of 50 patients (68% boys), median age 12 (0.4–21) years, were analysed (table 2). The patients were followed by 15 of the 28 centres with one to seven patients per centre, with 13 centres having no PPC patient treated with long-term NIV/CPAP at the time of the survey. All patients had complex and rare diseases with the most common diseases being disorders of the central nervous system (n=23, 46%), chromosomal anomalies (n=5, 10%) or peripheral neurological diseases (n=3, 6%) (table 2). Three patients were older than 18 years but were managed since childhood by a paediatric centre (one patient with Kenny Caffey syndrome, one patient with encephalopathy and one patient with fibrodysplasia ossificans progressiva). The patients had a median of three (two to six) PPC decisions with 'limitation of care' for 98% of the patients, 'do-not-intubate' for 72%, 'comfort care only' for 46%, with an advanced directive being available for 70% of the patients (table 3). Sixty-six per cent were managed by a PPC and 50% by a paediatric pain team. Opioids were prescribed to 36% of patients, analgesics to 48%, anxiolytics to 30% and melatonin to 20% for sleep problems (table 3). Sixty per cent of the patients had oxygen at home, 62% a pulse oximeter and 62% a suction equipment (table 3). Fifty per cent of the patients had an airway clearance device at home and 68% of the patients had a gastrostomy. Forty-six patients lived at home, 23 attended a specialised medical institution, 4 attended a specialised boarding school and 3 attended a normal school with a school life assistant.

A poly(somno)graphy (P(S)G) was performed prior to NIV/CPAP initiation in 44% of patients while 33% had only a nocturnal pulse oximetry (SpO₂) with a transcutaneous carbon dioxide pressure (PtcCO₂) recording (table 4).

The decision of NIV/CPAP initiation was taken on objective criteria in 78% of the patients (table 4): a high Apnoea-Hypopnea Index in 36% of patients, an abnormal nocturnal SpO₂ and PtcCO₂

Table 4 Investigations performed prior to NIV/CPAP initiation and NIV/CPAP initiation criteria

Investigations prior to NIV/CPAP initiation, n (%)	
PG/PSG	22 (44%)
Nocturnal SpO ₂ + PtcCO ₂ recording alone	16 (33%)
Nocturnal SpO ₂ recording (alone)	3 (6%)
NIV/CPAP initiation criteria, n (%)	
Apnoea-Hypopnea Index	18 (36%)
Nocturnal SpO ₂ + PtcCO ₂ recording alone	28 (56%)
Nocturnal SpO ₂ recording (alone)	2 (4%)
Nocturnal PtcCO ₂ recording alone	2 (4%)
Clinical criteria	
Acute respiratory failure requiring admission to the PICU	11 (22%)
Inspiratory dyspnoea	4 (8%)
Witnessed apnoeas	4 (8%)
Life-threatening respiratory event	1 (2%)
Before arthrodesis	1 (2%)
CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; PG, respiratory polygraphy; PICU, paediatric intensive care unit; PSG, polysomnography; PtcCO ₂ , transcutaneous carbon dioxide pressure; SpO ₂ , pulse oximetry.	

alone in 56% of patients, or one of these last two parameters in 8% of the patients. In 22% of the patients, NIV/CPAP was initiated during an acute respiratory failure, severe inspiratory dyspnoea (8%) or witnessed apnoeas (8%).

Sixty-four per cent of the patients were treated with NIV and 36% with CPAP. Mean CPAP level was 8±1.5 cm H₂O (table 5). For NIV, mean inspiratory and expiratory pressures were 16±5 cm H₂O and 7±2 cm H₂O, respectively, with a mean backup rate of 21±5 breaths/min. Mean objective adherence was excellent with a mean use of 9.3±3.7 hours/night (table 5). None of the patients used his NIV/CPAP less than 4 hours/night and only one patient used NIV >16 hours/day. The majority of patients (78%) used a nasal interface.

PROMs were available for 86% of the parents. Sixty per cent of these family/patients, reported that NIV/CPAP was associated with a decrease in their child's dyspnoea, 60% of parents reported an improvement in their child's sleep duration, 74% an improve-

Table 5 Duration of NIV/CPAP, NIV/CPAP adherence, equipment and settings

Duration of NIV/CPAP treatment, years	
	4.2±3.0
	3 (0.5–12)
Adherence (hours/night)	
	9.3±3.7
	10 (3–20)
<4 hours/night (n, %)	0 (0%)
≥16 hours/night (n, %)	1 (2%)
Interfaces	
Nasal (n, %)	39 (78%)
Nasobuccal (n, %)	9 (18%)
Total face (n, %)	2 (4%)
NIV, n (%)	
IPAP, cm H ₂ O	16±5
	14 (8–24)
EPAP, cm H ₂ O	7±2
	6 (4–10)
BUR, breaths/min	21±5
	20 (15–32)
CPAP, n (%)	
CPAP level, cm H ₂ O	8.0±1.5
	8 (6–14)

Data are given as mean±SD and median and range or number (percentage). BUR, backup rate; CPAP, continuous positive airway pressure; EPAP, expiratory pressure; IPAP, inspiratory pressure; NIV, non-invasive ventilation.

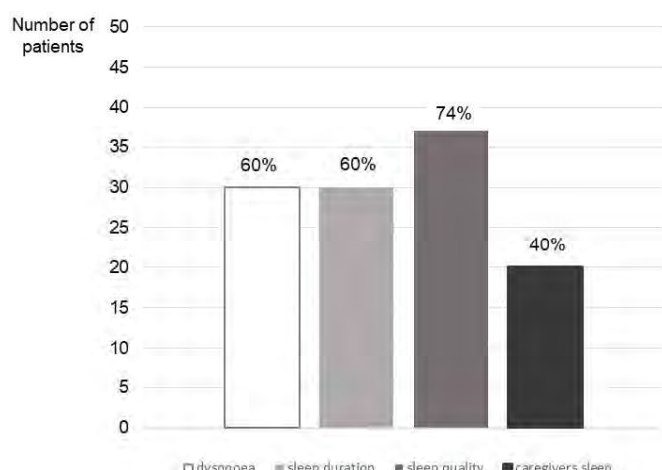


Figure 1 Patient-related outcomes in dyspnoea, sleep duration, sleep quality and parents' sleep reported by the family/patient. White bar: number of patients with an improvement in dyspnoea, light grey bar: number of patients with an improvement in sleep duration, dark grey bar: number of patients with an improvement in sleep quality, black bar: number of main caregivers with an improvement in sleep quality.

ment in their child's sleep quality, and 40% of the parents reported an improvement in their own sleep (figure 1). NIV/CPAP was also associated with a decrease in hospitalisations for respiratory episodes (n=12), in daytime fatigue with an increase in alertness (n=6), a decrease in respiratory secretions (n=2), a decrease in epileptic episodes (n=1), the withdrawal of daytime oxygen therapy (n=1) and an increase in weight (n=1). The improvement after NIV/CPAP did not differ according to the initiation after objective measurements or after a clinical evaluation only. Five (10%) patients died during the 4 months of the data collecting period.

DISCUSSION

This study is the first to show that long-term NIV/CPAP may be associated with a subjective improvement in patient's dyspnoea, sleep duration and sleep quality, and an improvement in parents' sleep, in children and young adults with complex life-limiting disorders and managed within a PPC or equivalent. All patients had rare and complex disorders, mainly of the central nervous system and an excellent objective adherence to NIV/CPAP.

This study explores a major area that is largely underdiagnosed and undertreated in children managed within a PPC. Fifty children were identified in this cross-sectional study, which represents approximately 3.5% of the total number of children treated with long-term NIV/CPAP in France, or 4.7% when excluding children with neuromuscular disease.⁸ This number is larger than the 19 children included in the Spanish study but comparable to the 47 children in the single-centre Italian study.¹² This may be explained by the fact that the Italian study and the present study were performed by paediatric pulmonologists who have been concerned with SDB and its management. However, given the extremely high prevalence of dyspnoea, SDB and sleep problems in children in PPC,² it is probable that SDB is underevaluated.

The diagnosis of SDB is challenging in children with life-limiting disorders. The patients are usually uncomfortable, the patient and the family may be reluctant to perform sophisticated exams like a PSG, and the cooperation of the child may be difficult as many children have disorders associated with a developmental delay and poor cooperation. This gives weight to simplified tools able to monitor sleep duration and sleep quality. Respiratory polygraphy may be an alternative to PSG.⁷ Abnormal nocturnal gas exchange may also justify NIV or CPAP on its own.^{7 10} Actigraphy has also been shown to be a valuable tool to assess sleep behaviour, sleep efficiency and abnormal breathing in eight children in PPC.¹¹ But NIV or CPAP may also be indicated in some clinical situations such as acute respiratory failure.⁷ In the present study, NIV/CPAP

was initiated on clinical criteria in 22% of the patients. A more systematic assessment of SDB is highly recommended in this population, at least on clinical symptoms, as the main objective of NIV/CPAP in PPC is to relieve dyspnoea and SDB symptoms.

The medical complexity of the patients is reflected by the underlying disorders and the multiple devices prescribed at home. Indeed, 62% of the patients had a disorder of the central nervous system, a chromosomal anomaly or a peripheral neurological disease (table 2). Sixty-eight per cent of the patients had nutritional problems requiring a gastrostomy. More than half of the patients had also 'as needed' oxygen therapy, guided by punctual SpO₂ measurements by means of a pulse oximeter. This high dependence on respiratory and non-respiratory technology is comparable to the experience of other paediatric centres.¹²

One of the major interests of our study is that NIV/CPAP was associated with a decrease in dyspnoea in 60% of the patients with an increase in sleep duration and sleep quality. These results are in line with the excellent objective NIV/CPAP adherence in patients of whom a majority have a developmental delay and behaviour problems. This high NIV/CPAP adherence may be an additional, indirect marker of the patients' comfort with NIV/CPAP.

Parental care for a child with a life-limiting condition is a complex physical and mental burden. Indeed, a recent review observed that caregiver health was negatively impacted in 84% of cases with pain and sleep problems being the most common problems,⁴ underlining the urgent need of interventions aimed at improving physical and mental health in caregivers.⁴ There seems also to be an association between patient-reported severity of symptoms and caregiver symptoms with sleep symptoms being among the most common complaints.¹² The improvement of dyspnoea and SDB by means of long-term NIV/CPAP in selected children with life-limiting conditions may thus be one tool to decrease the caregivers' burden.

As the study was performed within the French paediatric NIV network, the recruitment of the patients may be biased. Indeed, in the literature, the majority of PPC children have neurological diseases, oncological and haematological cancers, heart disease, or a variety of congenital and chromosomal abnormalities.^{1 2 4 11,13–15} The patients were cared by 15 centres with a limited number of patients per centre. Only 66% of the patients were managed by an official PPC. Indeed, as not every participating centre had a dedicated PPC, we made the choice to list a series of multidisciplinary decisions associated with a limitation of care. As this was a cross-sectional study including only patients treated with NIV/CPAP since at least 3 months, we have no information on the patients who were not proposed NIV or who did not tolerate or refused NIV/CPAP.⁷ The decision to initiate or not long-term NIV in children has been shown to be stressful for parents.¹⁶ Parents want comprehensive, balanced information on the impact of long-term NIV on their child but also on the family. When the child has a profoundly serious and life-limiting condition, they should have the option not to initiate long-term NIV.¹⁶ A shared decision with a NIV trial during a determined period allowing the evaluation of PROMs, may be an option in this situation. The benefit of NIV/CPAP was assessed by PROMs. And finally, information on the parent (mother or father) who responded to the questions, as well as their age, education and income level, was not available.

In conclusion, this study shows the high adherence and major subjective benefit of long-term NIV/CPAP in selected children and young adults with life-limiting disorders. This supports the inclusion of pulmonary paediatricians in the management of these patients and the usefulness to screen and treat dyspnoea, by means of autoassessment and heteroassessment tools for patients who are unable to communicate, and SDB with minimally invasive tools in these patients in order to minimise burden on patients and families.

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REFERENCES

- 1 Caggiano S, Pavone M, Cherchi C, et al. Children with medical complexity and pediatric palliative care: data by a respiratory intermediate care unit. *Pediatr Pulmonol* 2023;58:918–26.
- 2 Peláez Cantero MJ, Morales Asencio JM, Navarro Marchena L, et al. End of life in patients under the care of paediatric palliative care teams. Multicentre observational study. *An Pediatr (Engl Ed)* 2022;96:394–401.
- 3 Benini F, Papadatou D, Bernadà M, et al. International standards for pediatric palliative care: from Impact to GO-PPaCS. *J Pain Symptom Manage* 2022;63:e529–43.
- 4 Hartley J, Bluebond-Langner M, Candy B, et al. The physical health of caregivers of children with life-limiting conditions: a systematic review. *Pediatrics* 2021;148:e2020014423.
- 5 Avagnina I, Giacomelli L, Mercante A, et al. International project on troublesome symptoms in paediatric palliative care will focus on neuro-irritability, dystonia and sleep disorders. *Acta Paediatr* 2023;112:569–70.
- 6 Fauroux B, Pigeot J, Polkey MI, et al. In vivo physiological comparison of two ventilators used for domiciliary ventilation in children with cystic fibrosis. *Crit Care Med* 2001;29:2097–105.
- 7 Fauroux B, Abel F, Amadeo A, et al. ERS statement on pediatric long term noninvasive respiratory support. *Eur Respir J* 2022;59:2101404.
- 8 Fauroux B, Khirani S, Amadeo A, et al. Paediatric long term continuous positive airway pressure and noninvasive ventilation in France: a cross-sectional study. *Respir Med* 2021;181:106388.
- 9 Together for Short Lives. A guide to children's palliative care (fourth edition). 2018. Available: <https://www.togetherforshortlives.org.uk/wp-content/uploads/2018/03/TfSL-A-Guide-to-Children%E2%80%99s-Palliative-Care-Fourth-Edition-5.pdf>
- 10 Amadeo A, Moreau J, Frapin A, et al. Long term continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) in children: initiation criteria in real life. *Pediatr Pulmonol* 2016;51:968–74.
- 11 Kubek LA, Kutz P, Roll C, et al. Applicability of actigraphy for assessing sleep behaviour in children with palliative care needs benchmarked against the gold standard polysomnography. *J Clin Med* 2022;11:7107.
- 12 Mercadante S, Piccione T, Spinnato F, et al. Caregiver distress in home palliative care. *Am J Hosp Palliat Care* 2022;39:1337–41.
- 13 Mohammadi F, Zahra Masoumi S, Oshvandi K, et al. Death anxiety, resilience, and family cohesion in parents of children and adolescents in the end stages of life. *Front Psychol* 2023;14:1057003.
- 14 Andriastuti M, Halim PG, Tunjungsari E, et al. Home-based palliative intervention to improve quality of life in children with cancer: a randomized controlled trial. *Asian Pac J Cancer Prev* 2022;23:3029–34.
- 15 Toro-Pérez D, Camprodón-Rosanas E, Navarro Vilarrubí S, et al. Assessing well-being in pediatric palliative care: a pilot study about views of children, parents and health professionals. *Palliat Support Care* 2023;2023:1–9.
- 16 Edwards JD, Panitch HB, Nelson JE, et al. Decisions for long-term ventilation for children. Perspectives of family members. *Ann Am Thorac Soc* 2020;17:72–80.

ARTIGO ORIGINAL

Melhorando a desclassificação de alergias a beta-lactâmicos em doentes pediátricos hospitalizados: um estudo de melhoria da qualidade

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RESUMO

Objetivos: Avaliar a implementação de um programa liderado por uma equipa de vigilância antimicrobiana para a desclassificação de alergias a beta-lactâmicos em doentes pediátricos hospitalizados, utilizando testes de provocação oral direta (OPT).

Desenho: Estudo de melhoria da qualidade com duração de um ano, usando um desenho de antes-depois.

Local: Hospital pediátrico terciário independente.

Doentes: Doentes com alegações de alergia a beta-lactâmicos admitidos na unidade de internamento de medicina pediátrica.

Intervenções: Após avaliação padronizada e estratificação de risco dos sintomas relatados, os doentes com histórico de baixo risco foram submetidos a OPT. As etiquetas de alergia a beta-lactâmicos foram removidas se o histórico relatado fosse considerado não alérgico ou após um OPT bem-sucedido.

Principais medidas de resultado: Remoção de etiquetas inadequadas de alergia a beta-lactâmicos.

Resultados: Foram avaliados 80 doentes com 85 relatos de alergias a beta-lactâmicos. A idade mediana foi de 8,1 anos (IQR 4,8–12,9) e 34 (42%) eram do sexo feminino. A maioria (n=55, 69%) tinha uma condição médica subjacente. A amoxicilina foi a alergia mais relatada (n=25, 29%). As reações relatadas foram principalmente dermatológicas (n=65, 77%). Metade dos participantes (n=40) não eram elegíveis para OPT, em igual proporção por motivos clínicos ou pela natureza da reação relatada. Dos 40 doentes elegíveis, 28 (70%) foram desclassificados apenas com base no histórico (n=10) ou após OPT (n=18). Todos os OPTs foram bem-sucedidos. A desclassificação permitiu que cinco doentes adicionais (11% daqueles que receberam antibióticos) recebessem o beta-lactâmico preferencial. Incluindo os doentes posteriormente avaliados na clínica de alergia, quase metade de todos os doentes avaliados foram desclassificados (n=37, 46%).

Conclusões: Um programa liderado por uma equipa de vigilância antimicrobiana, utilizando OPT direto, mostrou-se viável e seguro para ampliar a desclassificação de alergias a beta-lactâmicos em doentes pediátricos admitidos na unidade de internamento de medicina pediátrica.

INTRODUCTION

Beta-lactam antibiotics are among the most prescribed medications in paediatric patients for many infections due to their consistent efficacy and tolerability.¹ Approximately 10% of the population report having a beta-lactam allergy, although 90% of these patients can tolerate them after formal allergy evaluation.^{1,2} Patients with a beta-lactam allergy label frequently receive alternative antibiotics that are less effective and more costly.¹ Having a beta-lactam allergy label is asso-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Self-reported beta-lactam allergies are often inaccurate and have negative individual and population health implications.
- Mounting evidence supports the safety and diagnostic accuracy of a direct oral provocation test (OPT) among those with low-risk histories in the paediatric allergy clinic setting.

WHAT THIS STUDY ADDS

- An antimicrobial stewardship program-led paediatric inpatient beta-lactam allergy de-labelling programme using an OPT was safe and feasible.
- The majority of reported reactions to oral beta-lactams (including cephalosporins and other penicillin-based antibiotics) were considered low risk.
- De-labelling during hospital admission yielded both immediate and short-term benefits to the care received by paediatric patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- With the increasing awareness of the potential harm and burden of inappropriate beta-lactam allergy labels, allergy specialists alone cannot meet this demand for assessments.
- Engaging antimicrobial stewardship programmes in paediatric beta-lactam allergy assessments can increase access to this essential service and allow for expansion to other clinical areas.

ciated with negative potential health consequences.¹ Since beta-lactam allergy labels are often acquired in childhood,² removing inappropriate labels (ie, de-labelling) in children may provide lifelong benefits.

After an appropriate history, patients reporting low-risk reactions can safely receive a direct oral

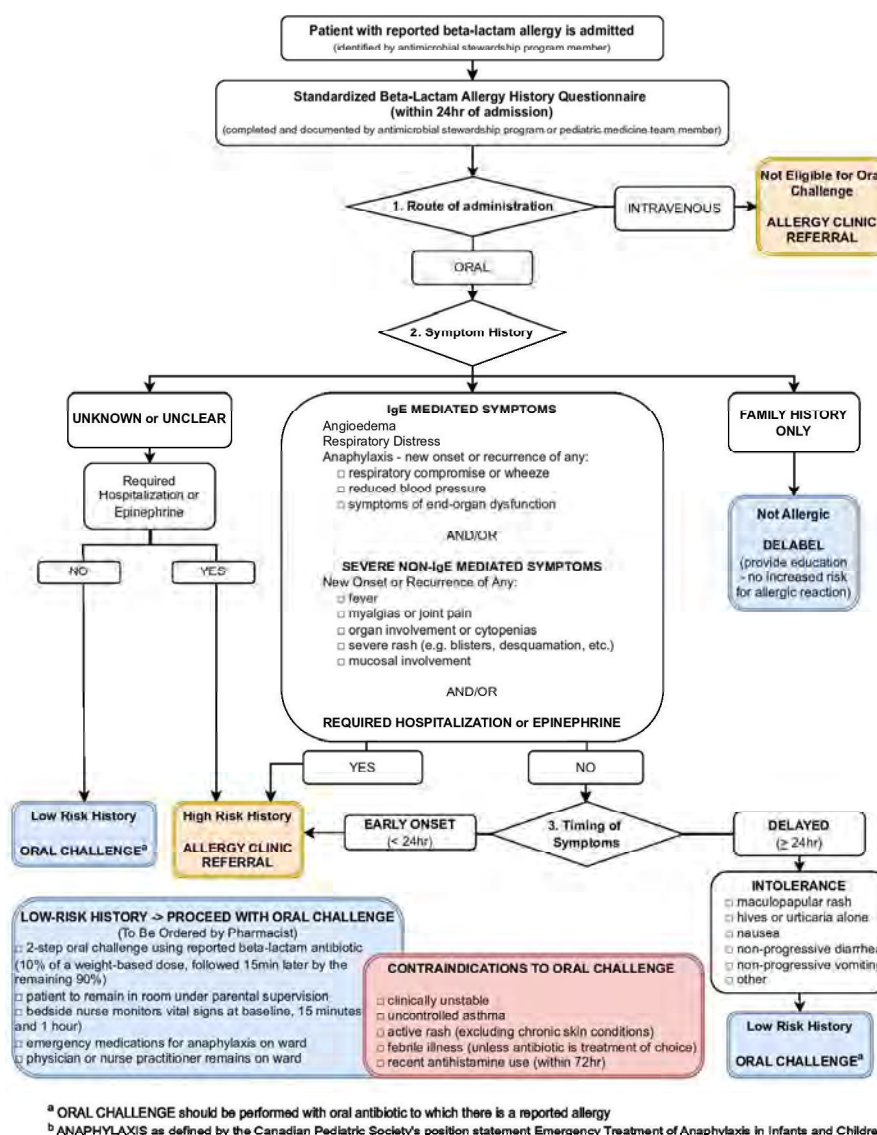


Figure 1 De-LABEL Programme overview. ^aORAL CHALLENGE to be performed with oral antibiotic to which there was a reported allergy. ^bANAPHYLAXIS as defined by the Canadian Paediatric Society's position statement Emergency Treatment of Anaphylaxis in Infants and Children. ⁷ De-LABEL, De-Labeling of Allergies to Beta-Lactams.

provocation test (OPT) with amoxicillin or penicillin.² Antimicrobial stewardship programmes aim to improve the appropriate use of antimicrobials and are well positioned to increase the availability of beta-lactam allergy testing.² The primary objective of this quality improvement project was to evaluate the implementation of an antimicrobial stewardship programme-led inpatient beta-lactam allergy de-labelling programme using a direct OPT on the paediatric medicine inpatient unit.

METHODS

The De-Labeling of Allergies to Beta-Lactams Programme

In collaboration with the Divisions of Allergy and Immunology, Infectious Diseases and Pharmacy, a De-Labeling of Allergies to Beta-Lactams (De-LABEL) Programme using a direct OPT was developed in 2018 (figure 1). An antimicrobial stewardship programme member identified inpatients with a reported beta-lactam allergy on their electronic medical record (EMR) and conducted a standardised beta-lactam allergy assessment (online supplemental table 1). Reported symptoms were risk stratified as non-allergic, low risk or high risk. Patients with low-risk reactions and no contraindications were offered a two-step OPT during the admission (online supplemental figure 1). Those with high-risk reactions or contraindications were referred to allergy clinic. Beta-lactam allergy labels were removed from the EMR if a patient was considered non-allergic based on history or after successful OPT.

Study design

We performed a single-centre quality improvement study using a before–after design, prior to which patient beta-lactam allergies were not routinely assessed. Following the De-LABEL Programme implementation, we prospectively enrolled patients with a beta-lactam allergy on their EMR admitted to the paediatric medicine inpatient unit over a 1-year period (23 January 2018–22 January 2019). Clinical information and inpatient antibiotic use were extracted from EMRs. The primary outcome was the removal of inappropriate beta-lactam allergy labels from the EMR. Inpatient de-labelling was reported monthly and summarised as a proportion with corresponding CI, then compared with a historical cohort of patients admitted to the paediatric medicine inpatient unit (1 January 2016–31 December 2016).³ We consulted the Standards for Quality Improvement Reporting Excellence 2.0 guidelines in the formulation of this report.⁴

RESULT

During the study period, 3674 patients were admitted to the paediatric medicine inpatient unit including 109 with a reported beta-lactam allergy. 80 patients underwent a standardised beta-lactam allergy assessment (73%) (online supplemental table 2). Median age was 8.1 years (IQR 4.8–12.9) and 34 (42%) were female. The majority (n=55, 69%) had an underlying medical condition, of which 31 (56%) were children with medical complexity. 75 patients reported a single beta-lactam allergy (94%), 5 patients reported more than one

Table 1 Reported beta-lactam allergy characteristics (N=85)

Variable	n
Reported beta-lactam allergies	
Penicillin class	7
Specific penicillin agents (55 reported beta-lactam allergies)	
Amoxicillin	25
Amoxicillin–clavulanic acid	4
Ampicillin*	2
Penicillin	18
Piperacillin–tazobactam*	6
Specific cephalosporin agents (23 reported beta-lactam allergies)	
Cefazolin*	1
Cefprozil	7
Ceftriaxone*	10
Cefuroxime	1
Cephalexin	4
Reported beta-lactam reaction†	
Non-allergic (6 reported beta-lactam allergies)	
Family history alone	0
Intolerance‡	6
Low-risk (62 reported beta-lactam allergies)	
Isolated hives/urticaria	10
Non-urticarial rash	11
Rash (not otherwise specified)	35
Other (not requiring hospitalisation)§	6
High-risk (17 reported beta-lactam allergies)	
Anaphylaxis	5
Angioedema	1
Hives/urticaria within 24 hours	7
Rash (severe)¶	2
Systemic**	2

*Intravenous formulation.

†May have reported more than one reaction within the category.

‡Gastrointestinal symptoms, avoided due to history of gallstones or nephrocalcinosis.

§Family could not recall reaction (five patients), developed gallstones while receiving ceftriaxone (one patient).

¶Bullous lesions, blisters, diffuse swelling, skin peeling.

**Haemolytic anaemia, new-onset fever over 40°C.

beta-lactam allergy (6%) and 9 patients also reported other antibiotic allergies (11%). Reported reactions are described in table 1. Two-thirds of reported reactions involved penicillins (n=55, 71%) and the most reported allergen was amoxicillin (n=25, 29%). Low-risk dermatological reactions were the most frequently reported reaction (n=56, 66%). High-risk histories (n=17, 20%) included five reports of anaphylaxis.

40 patients were eligible for OPT (figure 2), with a median of 2 patients each month (range 0–10). Over two-thirds of eligible patients were de-labelled as inpatients (n=28, 70% (95% CI 53.47%, 84.45%)), 10 based on history alone and 18 with OPTs. All OPTs were successful without any immediate reactions or unplanned emergency department (ED) visits. Pre-intervention, none of the 76 patients with reported beta-lactam allergies were de-labelled. Following implementation of the De-LABEL Programme, the proportion of eligible inpatients de-labelled significantly changed from baseline ($p<0.000$) (figure 3). 16 patients not eligible for an inpatient OPT were subsequently assessed in the allergy clinic. An additional nine patients were de-labelled; four patients had their beta-lactam allergy confirmed and three patients could not have a true beta-lactam allergy ruled out due to insufficient clinical information or incomplete testing. Overall, almost half of the 80 patients assessed during the study were de-labelled (n=37, 46%). 14 patients presented to hospital (eg, ED, clinic visit, hospital admission) within the following year, and none of the beta-lactam allergy labels reappeared.

Antibiotic treatment was indicated in 46 (58%) patients at the time of their beta-lactam allergy assessment (online supplemental table 3). Where beta-lactams were the recommended therapy based on

hospital guidelines, 26 patients (67%) were receiving the preferred antibiotic (which differed from the reported beta-lactam allergy). De-labelling allowed five additional patients to receive the preferred beta-lactam (n=31 of 40, 78%), including stepdown to a narrow-spectrum oral antibiotic. In the year following their beta-lactam allergy assessment, 22 patients received antibiotics during subsequent admissions, including 11 who were previously de-labelled. Patients were more likely to receive the preferred beta-lactam if they were previously de-labelled (n=8 of 9, 89%) compared with those who were not (n=4 of 9, 44%).

DISCUSSION

We demonstrated that an antimicrobial stewardship programme-led programme for routine assessment and systematic removal of inappropriate beta-lactam allergy labels appropriately identified eligible patients, with all patients who underwent an OPT successfully being de-labelled. 70% of eligible patients were de-labelled as inpatients, and none of the beta-lactam allergy labels reappeared. Consequently, an additional 12% of patients receiving antibiotics had their therapy optimised.

We found 80% of reported reactions were either low risk or not in keeping with an allergy, and all patients who underwent an OPT were de-labelled successfully. Our experience aligns with literature from the paediatric allergy clinic setting.² Bauer et al recently described their clinical care pathway to assist physicians in identifying and de-labelling inappropriate penicillin allergies among low-risk paediatric inpatients.⁵ They de-labelled 11.7% of patients who reported a penicillin allergy. In comparison, we de-labelled 26% of patients

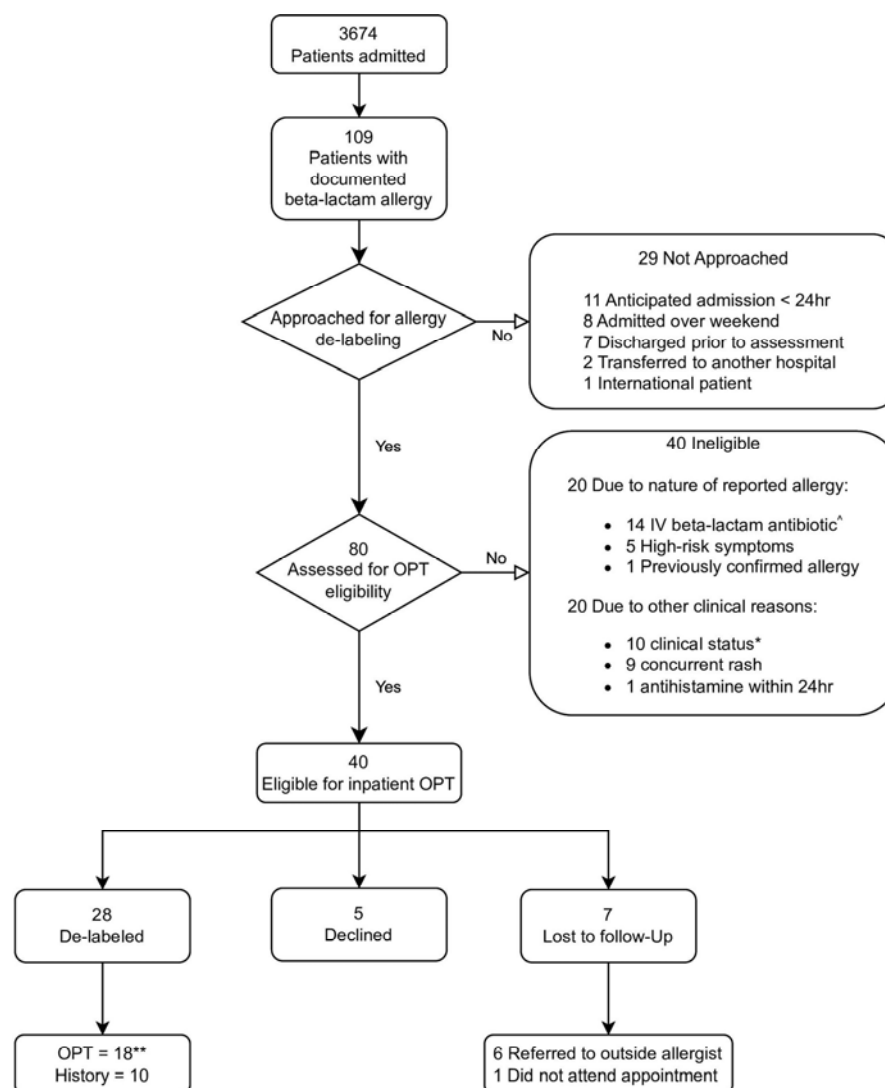


Figure 2 Included participants. *Including five patients with high-risk symptoms. *Clinical status=fever and /or instability (six patients), profuse/bloody diarrhoea (one patient), planned procedure (one patient), concurrent intravenous antibiotics (one patient), parent/caregiver not available to remain at bedside (one patient). **Two patients were de-labelled in the allergy clinic due to reasons of logistic and family preference. IV intravenous; OPT, oral provocation test.

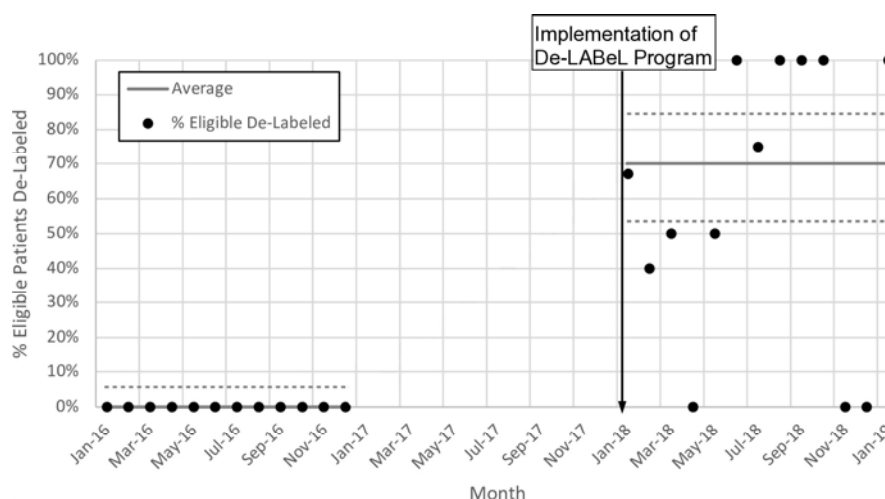


Figure 3 Inpatient de-labelling. Time series graph showing the proportion of admitted patients eligible to receive a direct oral provocation test who were de-labelled each month. Includes the time period prior to and during the current study. De-LABEL, De-Labeling of Allergies to Beta-Lactams.

who reported a beta-lactam allergy during admission, including a similar proportion after OPT. Our antimicrobial stewardship programme-led approach may have improved identification of patients, assessment and testing of reported beta-lactam allergies. Furthermore, using an OPT for all reported oral beta-lactams (including first and second-generation cephalosporins) increased the number of patients who were eligible for inpatient de-labelling.

The economic impact of routine paediatric inpatient beta-lactam allergy assessments has not been previously described in the Canadian context. In Ontario, we estimated a direct healthcare system cost of \$C202 (US\$145) for each allergy clinic assessment and OPT testing (including physician services and antibiotic dose).⁶ Assuming all de-labelled inpatients would have been referred to an allergist, we estimate cost-savings of over \$C5000 during this 1-year study by avoiding the need for 28 allergy clinic consultations and testing.

Limitations include the single-centre experience, the small population size and limited ability to assess future antibiotic use and reappearance of beta-lactam allergy labels. Strengths include the antimicrobial stewardship programme-led approach to routine inpatient paediatric beta-lactam allergy de-labelling and the use of a direct OPT for all reported oral beta-lactams.

CONCLUSION

Our antimicrobial stewardship programme-led programme using a structured beta-lactam allergy assessment tool and subsequent direct OPT where appropriate was feasible and safe for expanding beta-lactam allergy de-labelling to patients admitted to the paediatric medicine inpatient unit. De-labelling during hospital admission yielded both immediate and short-term benefits to the care received. Our experience builds upon existing paediatric literature focused on the use of amoxicillin or penicillin for direct OPTs, suggesting this approach is safe for oral first and second-generation cephalosporins as well.

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REFERENCES

- Abrams EM, Atkinson AR, Wong T, et al. The importance of Delabeling beta-lactam allergy in children. *J Pediatr* 2019;204:291–7.
- Vyles D, Antoon JW, Norton A, et al. Children with reported penicillin allergy: public health impact and safety of Delabeling. *Ann Allergy Asthma Immunol* 2020;124:558–65.
- Wong J, Torres M, Timberlake K, et al. Prevalence and impact of B-lactam allergies at a Canadian pediatric center. *Open Forum Infect Dis* 2018;5:S112.
- Ogrinc G, Davies L, Goodman D, et al. SQUIRE 2.0 (standards for quality improvement reporting excellence): revised publication guidelines from a detailed consensus process. *BMJ Qual Saf* 2016;25:986–92.
- Bauer ME, MacBrayne C, Stein A, et al. A Multidisciplinary quality improvement initiative to facilitate penicillin allergy Delabeling among hospitalized pediatric patients. *Hosp Pediatr* 2021;11:427–34.
- Ontario Ministry of Health. Schedule of benefits: physician services under the health insurance act. Ontario: Queen's Printer, June 2023.
- Cheng A. Emergency treatment of Anaphylaxis in infants and children. *Paediatrics & Child Health* 2011;16:35–40.

ARTIGO ORIGINAL

Não adesão relacionada ao custo aos medicamentos entre adultos com asma nos EUA, 2011–2022

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RESUMO

Contexto: A asma descontrolada pode estar relacionada à não adesão aos medicamentos, e as dificuldades financeiras podem ser um fator importante nessa não adesão. Como as condições econômicas e a gestão da asma mudaram ao longo do tempo, é essencial realizar uma investigação abrangente sobre a não adesão aos medicamentos relacionada ao custo (CRN) entre adultos com asma.

Objetivo: Avaliar tendências, prevalência e determinantes da CRN, bem como seu impacto no controle da asma em adultos nos EUA.

Métodos: Foram utilizados dados da National Health Interview Survey de 2011 a 2022. A análise de regressão joinpoint foi empregada para avaliar as tendências na prevalência de CRN. Um modelo de regressão logística multivariada foi utilizado para identificar fatores associados à CRN. Outros dois modelos de regressão logística multivariada examinaram as associações entre CRN e eventos adversos relacionados à asma, como ataques de asma e visitas às urgências por asma.

Resultados: Um total de 30.793 adultos com asma foram incluídos, representando 8,1% (19,38 milhões) da população dos EUA. De 2011 a 2022, foi observada uma tendência de queda na prevalência de CRN entre adultos com asma nos EUA. Aproximadamente um em cada seis adultos com asma não aderiu aos medicamentos devido ao custo. Diversos fatores, incluindo características demográficas e comorbidades, foram associados à CRN. Adultos com asma que apresentavam CRN tiveram um risco aumentado de ataques de asma (OR ajustado, 1,95; IC 95% 1,78 a 2,13) e de visitas às urgências por asma (OR ajustado, 1,63; IC 95% 1,44 a 1,84).

Conclusão: Sendo a asma uma das principais doenças crônicas, o impacto da não adesão aos medicamentos relacionada ao custo destaca a necessidade de políticas apropriadas e apoios sociais para enfrentar esses problemas.

INTRODUCTION

Asthma is one of the most common chronic diseases, affecting 5.4% of the population globally.¹ In 2021, the Centers for Disease Control and Prevention estimated that approximately 20.3 million adults (8.0%) had asthma in the USA. Asthma is an illness with a high economic burden on society, which accounted for \$81.9 billion in total costs in 2013.² Among healthcare expenses for asthma, prescribed medications were the most expensive types of care, constituting nearly half of asthma spending.³ Asthma can be properly managed with asthma medications.¹ The goals of asthma management are to achieve good symptom control and minimise risks of asthma-related mortality, exacerbations and side effects from treatment.¹ However, the prevalence of uncontrolled asthma remains high.² Patients with uncontrolled asthma face increased risks of adverse outcomes, including emergency room (ER) visits, hospitalisations, and absenteeism from school and work.¹

One factor that contributes to uncontrolled asthma is medication non-adherence.^{4–5} Adherence to asthma medications tends to be poor, with reported rates of non-adherence varying widely from 22% to 66%.^{5–7} A study with 5504 patients investigated the adherence with fluticasone/salmeterol combination therapy and showed that patients filled enough medication to cover about 22% of days in a 1-year follow-up period.⁶ Medication non-adherence is complex and multifactorial and represents a major issue in treating patients with asthma.⁴ Financial hardship is a major factor which leads to medication non-adherence.^{4–8} Previous studies suggest that individuals with a low income or low socioeconomic status were more likely to have asthma exacerbations.⁸ Patients might delay taking or even skip prescribed medications if they are unable to afford treatment costs.⁴ This phenomenon consequently results in cost-related non-adherence to medications (CRN) and adversely affects their asthma control.

Key messages

What is the key question?

► Financial hardship can be a major contributor to the non-adherence to medications.

What is the bottom line?

► There is a declining trend in cost-related medication non-adherence among US adults with asthma. Those who had cost-related medication non-adherence were at an increased risk of experiencing asthma attacks and emergency room visits because of asthma.

Why read on?

► These results suggest that healthcare providers can consider a collaborative approach by understanding patient's economic conditions and preferences before initiating the treatments.

The prevalence of CRN ranges 10%–25% among different chronic diseases in the USA.^{9–11} Prior evidence demonstrated that patients who reported CRN were at higher risk of hospitalisation and unplanned emergency visits than those without such problems.^{4–11} Several factors are associated with experiencing CRN, including age, sex, income and comorbidities.^{9–11} However, most previous studies conducted to investigate CRN were related to chronic diseases in general but were not specific to asthma. The extent to which CRN affects patients with asthma has not been well established. The determinants of CRN among individuals with asthma in the USA also remain unclear. Since economic conditions and medical management of asthma at the individual and population levels have changed over time,^{11,12} a better understanding of the trends in CRN is crucial in the USA, particularly given that

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a substantial proportion of the population has healthcare expenses far beyond their means.¹⁰

To bridge the study gap, this study aimed to (1) analyse the trend and prevalence of CRN, (2) investigate factors associated with CRN and (3) examine associations between CRN and asthma-related adverse outcomes among adults with asthma in the USA.

METHODS

Data source

We used data from the National Health Interview Survey (NHIS) from 2011 to 2022. Conducted by the National Center for Health Statistics (NCHS), the NHIS is a nationally cross-sectional survey which represents the US non-institutionalised population.¹³ Information of the NHIS is collected through questionnaires administered by trained interviewers from the NCHS.¹³ They collect a broad range of information including demographic, socioeconomic and health conditions.¹³ The NHIS uses a complex sampling design, which involves stratification, clustering and weighting to provide estimates for the non-institutionalised population in the USA.¹³ Data from the NHIS are publicly available as deidentified data through the NCHS.¹³

Study population

Adults with current asthma were included as the study population. We selected adult respondents aged 18 years or older from the Sample Adult file in the NHIS. Current asthma was defined as respondents who answered affirmatively to both of the following questions: 'Has a doctor or other health professional ever told you that you have asthma?' and 'Do you still have asthma?'.^{14 15}

Outcomes

In aims 1 and 2, CRN was the study outcome. CRN was defined as an affirmative response to any of the following questions: (1) 'Did you skip medication doses to save money over the past 12 months?'; (2) 'Did you take less medication to save money over the past 12 months?'; and (3) 'Did you delay refilling medications to save money over the past 12 months?'.^{9–11 15} These three questions were defined as the components of CRN.

In aim 3, asthma-related adverse events were the study outcomes, including asthma attacks and ER visits for asthma. Asthma attacks were identified by an affirmative response to the following question: 'During the past 12 months, have you had an episode of asthma or an asthma attack?'. ER visits for asthma were defined by an affirmative response to the following question: 'During the past 12 months, have you had to visit an emergency room or urgent care center because of asthma?'.¹⁴

Covariates

In this study, covariates were categorised into the following groups: age (grouped into 18–40, 41–60 and >60 years old), sex (male and female), race/ethnicity (non-Hispanic white, Hispanic, non-Hispanic black and others), region (Northeast, Midwest, South and West), educational level (less than high school and high school/higher), health insurance (not covered and covered), poverty status, representing family incomes as multiples of the federal poverty level (FPL) (<100%, 100%–<200%, 200%–<400% and ≥400%), work status (employed and unemployed), smoking status (non-smoker, former smoker and current smoker), perceived health status (good and poor), marital status (married or living with partner and single or living alone) and comorbidities (obesity (body mass index of ≥30 kg/ m²), hypertension, diabetes mellitus, coronary artery disease, hypercholesterolaemia, chronic obstructive pulmonary disease, liver disease, kidney disease and cancer).

Statistical analyses

Statistical analyses were implemented for each of the study aims. In aim 1, we estimated the prevalence and trend of CRN among US adults with asthma from 2011 to 2022. To obtain national estimates, survey-weighted proportions were used based on analytic guidelines of the NHIS.¹³ A joinpoint regression analysis was used

to evaluate the statistical significance of the trend in CRN during the study period.¹⁶ The average annual percentage change (AAPC) was determined with a joinpoint regression analysis, and we reported whether the AAPC was significantly different from zero.¹⁶ In aim 2, the Rao-Scott χ^2 test was used to assess differences in covariates among adults with asthma who reported CRN and those who did not. In addition, a multivariable logistic regression was used to investigate factors associated with reporting CRN. In aim 3, multivariable logistic regression models were used to examine associations between CRN and asthma-related adverse events, including asthma attacks and ER visits for asthma. Statistical significance was assessed with a two-tailed alpha of 0.05. The joinpoint regression analyses were performed with the Joinpoint Regression Program by the National Cancer Institute, V5.0.2.¹⁷ Other analyses were performed with survey-specific tools using Stata, V18.0 (StataCorp).

Sensitivity analysis

To test the robustness of our study results, we conducted several sensitivity analyses. The three components of CRN were evaluated separately for each aim. In aim 1, we estimated trends in the prevalence of each component of the CRN separately. In aim 2, multivariable logistic regression models were used to assess factors associated with each component of the CRN. In aim 3, multivariable logistic regression models were used to examine associations between each component of the CRN and asthma-related adverse events.

Subgroup analysis

To identify a group that might benefit most from targeted policies or interventions, we conducted a subgroup analysis for Aim 1. Trends in the prevalence of CRN were stratified by respondents' region (Northeast, Midwest, South and West).

RESULTS

The 2011–2022 NHIS included 378 350 sample adults. Among them, 30 793 adults had asthma, representing approximately 8.1% (19.38 million) of the US population. Table 1 shows the weighted prevalence of CRN from 2011 to 2022 among US adults with asthma. Overall, 17.8% of US adults with asthma reported CRN, representing an estimated 2.99 million of the US population. Among the components of CRN, 11.6% (1.95 million) of US adults with asthma skipped medication doses to save money, 12.4% (2.06 million) took less medication to save money and 15.1% (2.54 million) delayed refilling medications to save money. Figure 1 and online supplemental table 1 show the trend in prevalence of CRN from 2011 to 2022 among US adults with asthma. The prevalence of CRN significantly decreased during the 12-year period (AAPC=−5.0, 95% CI −6.1 to −3.8), with a decline from 23.2% in 2011 to 13.1% in 2022. In sensitivity analyses, this declining trend was also observed in each component of CRN (skipped medication doses to save money: AAPC=−6.5, 95% CI −7.9 to −5.1; took less medication to save money: AAPC=−6.2, 95% CI −7.3 to −5.1; and delayed refilling medications to save money: AAPC=−5.1, 95% CI −6.2 to −4.0). Online supplemental table 2 provides detailed results from the joinpoint regression analyses.

Table 1 Prevalence of cost-related non-adherence to medications among US adults with asthma

Outcomes	n*	N†	%‡	SE§
Cost-related non-adherence to medications	5045	2 985 882	17.8	0.3
Skipped medication doses to save money	3286	1 949 192	11.6	0.2
Took less medication to save money	3567	2 077 063	12.4	0.2
Delayed refilling medications to save money	4303	2 536 432	15.1	0.3

*n: the number of the unweighted population.

†N: the number of the weighted population.

‡%: the percentage of the weighted population.

§SE: the SE of the percentage.

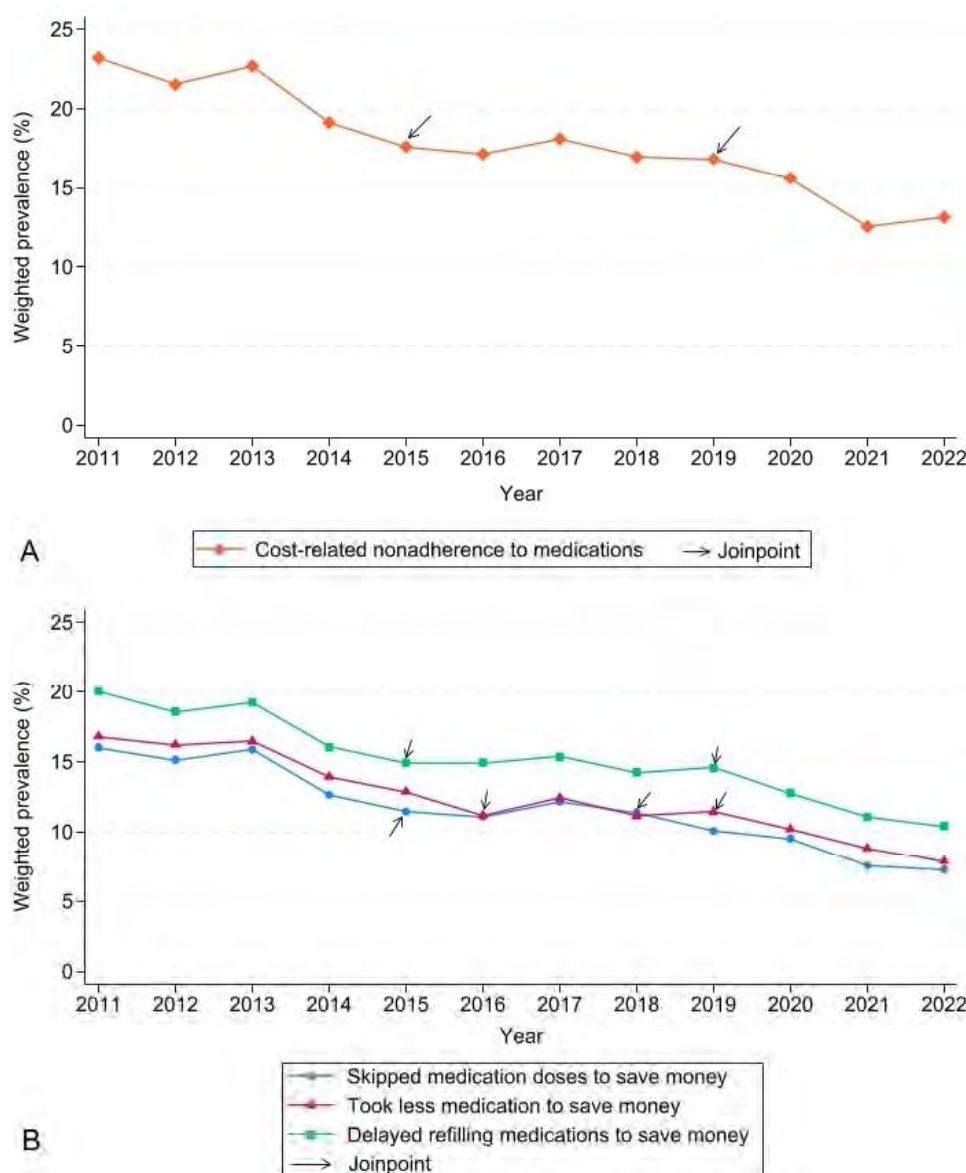


Figure 1 Trends in the prevalence of cost-related non-adherence to medications among US adults with asthma. Arrows indicate the joinpoints identified from joinpoint regression analyses. (A) Overall. (B) By components of cost-related non-adherence to medications.

Table 2 demonstrates the characteristics of US adults with asthma. Adult patients with asthma aged over 60 years were the least likely to report CRN compared with those aged 18–40 and 41–60 years (21.5% vs 18.7% and 21.5%, $p < 0.01$). Females were more likely to report CRN than males (19.5% vs 14.4%, $p < 0.01$). Among the race/ethnicity groups, non-Hispanic blacks were the most likely to report CRN. In addition, characteristics significantly associated with higher percentages of CRN included residing in the South, having an educational level of less than high school, lacking health insurance coverage, having a family income of 100%–<200% of the FPL, being a current smoker, having poor perceived health status and being single or living alone. As to comorbidities in adults with asthma, liver disease was the most commonly reported among those who experienced CRN. Patients with two or more comorbidities were the most likely to report CRN compared with those with one comorbidity and those with no comorbidities (20.3% vs 16.4% and 14.3%, $p < 0.01$).

Figure 2 and online supplemental table 3 present results of the multivariable logistic regression model. After the adjustment for all covariates and the survey year, patients with asthma who were younger, female, resident of the Midwest, South or West, with an educational level of less than high school, without health insurance coverage, with a family income of <400% of the FPL, a current or former smoker and with comorbidities were associated

with higher odds of reporting CRN. Those with a good perceived health status were associated with lower odds of reporting CRN. In the sensitivity analysis, we investigated factors associated with the three components of CRN (online supplemental table 4). Results were similar to those in the main analysis and showed that age, sex, region, educational level, health insurance coverage, family income, work status, smoking status, perceived health status and comorbidities were predictors for reporting CRN.

Figure 3 shows associations between CRN and asthma-related adverse events. More than half of the patients reporting CRN experienced asthma attacks. Approximately 19.0% of patients reporting CRN visited the ER for asthma. Adults with asthma who reported CRN had significantly higher odds of having asthma attacks (adjusted OR, 1.95; 95% CI 1.78 to 2.13) and ER visits for asthma (adjusted OR, 1.63; 95% CI 1.44 to 1.84) compared with patients without CRN. These results were consistent with those in the sensitivity analysis examining the three components of CRN (online supplemental table 5). Adults with asthma who skipped medication doses, took less medication and delayed refilling medications to save money had nearly two times the odds of having an asthma attack than those without CRN. Similarly, adults with asthma who reported any components of CRN had approximately 1.6-times higher odds of visiting the ER for asthma than those without CRN.

Table 2 Characteristics among US adults with asthma: descriptive statistics

Characteristic	Cost-related non-adherence to medications						P value
	Yes (N*=2 985 882)			No (N*=13 783 671)			
	N*	%†	SE‡	N*	%†	SE‡	
Age (years)							<0.01
>60	559 219	11.9	0.4	4 132 697	88.1	0.4	
41–60	1 291 693	21.5	0.5	4 717 495	78.5	0.5	
18–40	1 134 970	18.7	0.5	4 933 479	81.3	0.5	
Sex							<0.01
Male	818 294	14.4	0.5	4 848 887	85.6	0.5	
Female	2 165 415	19.5	0.4	8 934 784	80.5	0.4	
Race/ethnicity							<0.01
Non-Hispanic white	1 967 267	17.1	0.3	9 507 288	82.9	0.3	
Hispanic	396 868	20.1	1.0	1 577 580	79.9	1.0	
Non-Hispanic black	483 243	20.3	0.8	1 898 712	79.7	0.8	
Others	138 504	14.8	1.2	800 091	85.2	1.2	
Region§							<0.01
Northeast	416 307	12.9	0.6	2 801 682	87.1	0.6	
Midwest	715 204	18.9	0.6	3 072 339	81.1	0.6	
South	1 199 986	20.6	0.5	4 638 322	79.4	0.5	
West	654 384	16.7	0.6	3 271 329	83.3	0.6	
Educational level							0.05
Less than high school	336 198	19.4	0.9	1 392 860	80.6	0.9	
High school and higher	2 649 684	17.6	0.3	12 390 811	82.4	0.3	
Health insurance							<0.01
Covered	2 394 919	15.5	0.3	13 065 954	84.5	0.3	
Not covered	590 963	45.2	1.4	717 717	54.8	1.4	
Poverty status§							<0.01
FPL≥400%	507 379	8.8	0.4	5 226 113	91.2	0.4	
FPL 200%–<400%	890 731	20.7	0.6	3 421 616	79.3	0.6	
FPL 100%–<200%	794 491	25.8	0.8	2 290 380	74.2	0.8	
FPL<100%	655 221	23.2	0.8	2 173 231	76.8	0.8	
Work status							0.94
Employed	1 669 691	17.8	0.4	7 697 346	82.2	0.4	
Unemployed	1 316 191	17.8	0.4	6 086 325	82.2	0.4	
Smoking status							<0.01
Non-smoker	1 455 976	15.2	0.4	8 120 116	84.8	0.4	
Former smoker	734 748	17.1	0.6	3 572 931	82.9	0.6	
Current smoker	795 158	27.6	0.8	2 090 624	72.4	0.8	
Perceived health status							<0.01
Poor	463 608	30.4	1.2	1 063 210	69.6	1.2	
Good	2 522 274	16.5	0.3	12 720 461	83.5	0.3	
Marital status							<0.01
Married or living with partner	1 562 586	17.0	0.4	7 608 567	83.0	0.4	
Single or living alone	1 423 296	18.7	0.4	6 175 104	81.3	0.4	
Comorbidities							
Obesity (BMI≥30 kg/m²)	1 576 056	20.2	0.5	6 210 122	79.8	0.5	<0.01
Hypertension	1 427 033	19.8	0.5	5 786 966	80.2	0.5	<0.01
Diabetes mellitus	628 362	23.7	0.9	2 017 478	76.3	0.9	<0.01
Coronary artery disease	241 929	19.6	1.0	991 460	80.4	1.0	<0.01

Continued

Table 2 Continued

Characteristic	Cost-related non-adherence to medications						P value
	Yes (N*=2 985 882)			No (N*=13 783 671)			
	N*	%†	SE‡	N*	%†	SE‡	
Hypercholesterolaemia	1 020 311	18.9	0.5	4 377 896	81.1	0.5	<0.01
Chronic obstructive pulmonary disease	670 688	23.5	0.8	2 181 128	76.5	0.8	<0.01
Liver disease	119 251	28.8	2.0	295 004	71.2	2.0	<0.01
Kidney disease	148 166	26.8	1.9	405 432	73.2	1.9	<0.01
Cancer	386 603	18.7	0.8	1 684 646	81.3	0.8	<0.01
Comorbidities, n							<0.01
0	597 336	14.3	0.6	3 589 790	85.7	0.6	
1	709 205	16.4	0.6	3 615 973	83.6	0.6	
≥2	1 679 341	20.3	0.4	6 577 908	79.7	0.4	

*N: the number of the weighted population.
†%: the percentage of the weighted population.
‡SE: the SE of the percentage.
§Missing data due to the non-response rate (participants who answered ‘refused’, ‘not ascertained’ or ‘don’t know’) were low in our study, and we did not attempt to implement an imputation for those respondents.
BMI, body mass index; FPL, federal poverty level.

In the subgroup analysis, decreasing trends in the prevalence of CRN over time were found across all regions among patients with asthma. Notably, those residing in the South exhibited the smallest decline in CRN prevalence (AAPC=−5.0, 95% CI −7.0 to −3.2) (online supplemental tables 6 and 7).

DISCUSSION

Using nationally representative data, we provided insights into the prevalence, trend, factors and impacts of CRN among patients with asthma. We found that nearly one in six patients with asthma was non-adherent to medications due to cost. Over the past 12 years, there has been a declining trend in the prevalence of CRN among patients with asthma in the USA. Several factors, including demographics and comorbidities, were associated with CRN among asthma patients. Patients with CRN were at a high risk of experiencing asthma-related adverse events.

In this study, we estimated that 17.8% of patients with asthma experienced CRN, which was higher than the prevalence observed in patients with other chronic diseases.^{9–10} Kang et al used Behavioral Risk Factor Surveillance System data from 2013 to 2014 and found that 16.5% of US adults with diabetes experienced CRN.⁹ Previous studies have showed that adherence to medications was poor in patients with asthma.^{5–7} With a nationally representative population, our findings support that cost might be an important consideration. Xia et al also reported that 15.8% of patients with a history of asthma were non-adherent to medications due to cost considerations, which was comparable to our estimates.¹⁵ The present study reinforces the recommendation that patients with asthma are best controlled when they are prescribed and take medications that are strongly recommended by clinical guidelines.¹

From 2011 to 2022, we observed a declining trend in the prevalence of CRN among patients with asthma. This trend might be attributed to healthcare policies in the USA. In 2010, the Patient Protection and Affordable Care Act was enacted which aimed to improve access to health insurance and services.^{12–18} A significant strategy in the Affordable Care Act was the expansion of Medicaid, up to 138% of the FPL, with the aim of improving health outcomes for minorities.^{12–18} Shi et al found that Medicaid expansion was associated with increased utilisation of asthma medications among low-income patients with asthma in the USA from 2007 to 2018.¹² With fewer barriers to accessing healthcare, including medications, patients may be more willing to fill prescriptions for medications to control their asthma than before, potentially leading to a decrease in CRN.¹⁸ Further research comparing data before and after the implementation of the Affordable Care Act

is needed to evaluate its impact on CRN among patients with asthma.

Our findings showed that female sex and younger age were associated with CRN, which were consistent with previous studies.^{9–11,15} Our findings add to evidence that the gender disparity remains an issue in CRN among patients with asthma. Although younger patients might have fewer medical problems and be actively employed,¹⁹ they still had nearly two times the odds of experiencing CRN. Possible explanations could be lower earnings, making it harder to cover healthcare costs, or because they are less likely to be in a marriage or partnership where health responsibilities are shared. Adults aged 30–44 are more likely to be enrolled in high deductible health plans, which require individuals to pay more out of pocket for healthcare needs until the deductible is met.²⁰ These health plans are often associated with greater cost-related non-adherence.²¹ We found that low-income or uninsured patients with asthma were at increased risk for CRN. In such vulnerable populations, financial hardships could contribute to non-adherence. They might try to skip or reduce medication doses to save money.²² Without health insurance coverage, the cost of prescribed medications could result in higher out-of-pocket expenses for them, making it more challenging to afford necessary healthcare utilisation. Notably, patients with 100%–200% of FPL had the greatest CRN. This near-poor population often does not qualify for Medicaid in the USA, which might increase barriers to access healthcare.^{23–24} For example, a US national report showed that 23.9% of near-poor individuals were uninsured, compared with 26.2% of the poor population.²³ Decreased health insurance coverage might make near-poor patients more vulnerable to CRN.²³ Therefore, targeted policies to support this near-poor population with asthma are warranted to ensure that they are not left behind.

In our study, we found patients residing in the South and Midwest were associated with increased odds of experiencing CRN. Additionally, individuals from the South exhibited the highest CRN prevalence in most study years and the smallest decline in prevalence, which might be explained by differences in access to healthcare across geographical regions.^{25–26} People living in the South, particularly in rural areas, might face reduced healthcare utilisation due to financial burdens.²⁶ Furthermore, residence in the South was associated with an increased risk of uncontrolled asthma,²⁵ which is possibly reflected by the increased CRN rates observed among Southern residents. Therefore, targeted policies or interventions to reduce CRN may consider prioritising those residing in the South. Patients with asthma who had lower educational levels reported CRN more frequently than those with

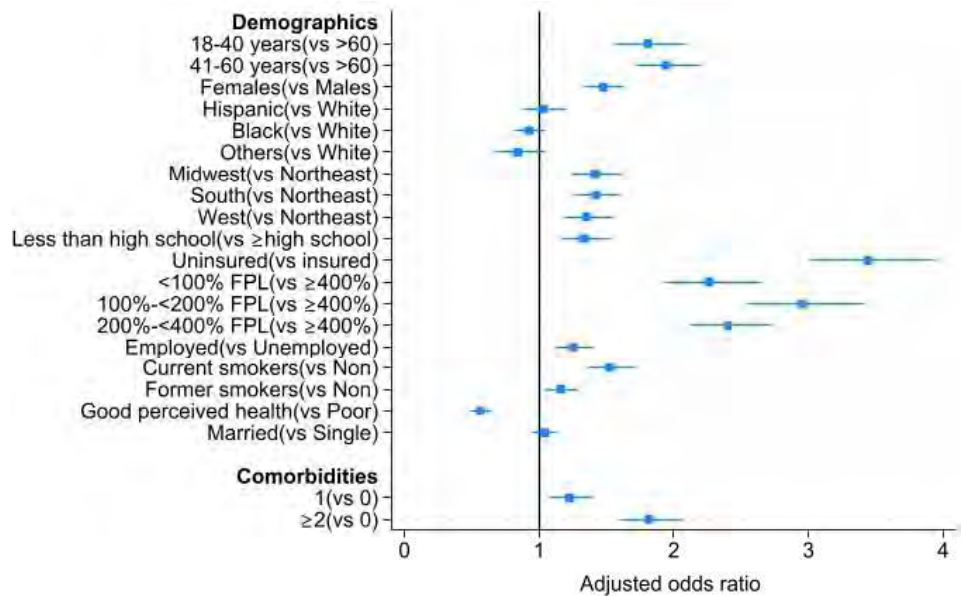


Figure 2 Characteristics associated with cost-related non-adherence to medications among US adults with asthma. FPL, federal poverty level.

higher educational levels. The level of education is associated with a number of factors that impact health outcomes, including health literacy.²⁷ Patients with a low health literacy might not be aware of the importance of routine medication use for their asthma control. This finding also underscores the need for healthcare providers to actively encourage their patients to take prescribed medications regularly for better asthma control. In this study, we demonstrated that asthma patients with comorbidities were more likely to experience CRN than those without comorbidities. This finding aligns with previous research on patients with other chronic diseases.⁹⁻¹¹ Patients with comorbidities often experience a high pill-burden.^{28,29} This problem not only causes high medication expenses but also discourages them from taking medications on time,²⁸ ultimately leading to medication non-adherence due to costs. These findings underscore the need for health policy interventions to alleviate financial constraints due to medication expenses. Future studies can also investigate the financial burden of patients with asthma who experienced CRN.

Our study demonstrated that patients with asthma who experienced CRN are at increased risk of asthma-related adverse events, including asthma attacks and ER visits. This finding was consistent with previous studies.^{30,31} Williams et al showed that 24% of asthma

exacerbations were attributable to non-adherence to inhaled corticosteroids.³⁰ Focusing on cost considerations, our results revealed that non-adherence was still an issue in poor asthma control. For healthcare providers, it is imperative to monitor patient's adherence to medications to prevent asthma exacerbations, especially when treating patients with financial concerns. As the continuous use of asthma medications is associated with substantial costs in the long run,^{2,32} understanding patient's economic conditions and preferences is important. For example, shared decision-making with patients before initiating treatments can serve as a valuable approach.³³ This collaborative process allows patients to choose medications that are affordable, potentially improving adherence and achieving better asthma control. Moreover, employing real-time prescription benefit tools to provide prescribers with patient-specific drug pricing and alternatives at the point of prescribing could be beneficial.³⁴ These tools may help improve medication adherence and reduce prescription drug costs,³⁴ ultimately leading to a decrease in CRN.

Our findings also carry important policy implications. First, healthcare policies related to frequently monitor CRN rates are necessary, particularly for underserved populations with asthma, such as those without health insurance or living in the South. Fur-

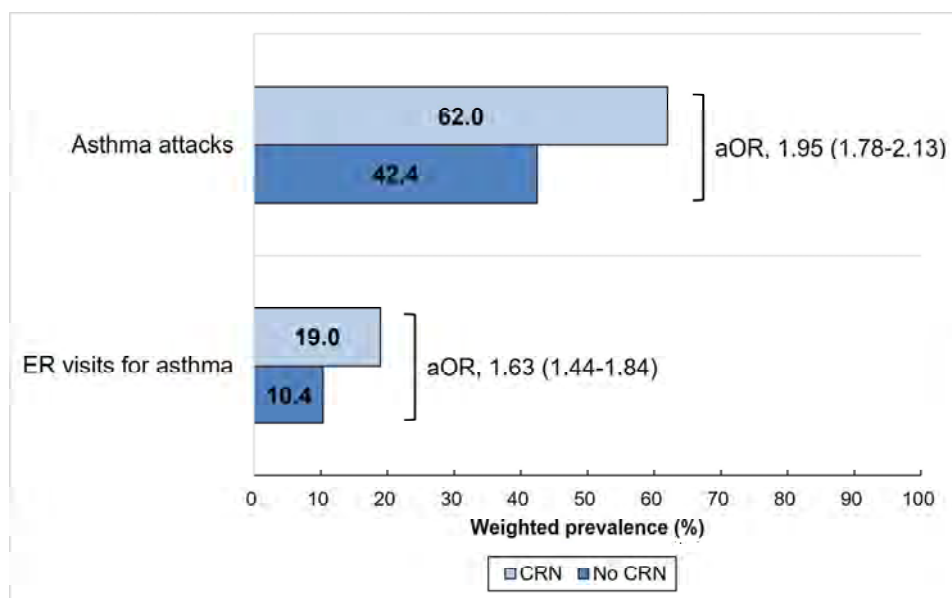


Figure 3 Associations between cost-related non-adherence to medications and asthma-related adverse events among US adults with asthma. aOR, adjusted OR; CRN, cost-related medication non-adherence; ER, emergency room.

thermore, collaboration with public health experts can help establish targeted CRN prevalence goals to be achieved through policy interventions. Reducing CRN may not only improve asthma control but also alleviate the financial burden on the healthcare system.³⁵ In 2002, the annual cost of non-adherence among patients with asthma to the US healthcare system was estimated at \$300 billion.³⁵ A US study further demonstrated that a 25% improvement in adherence was associated with a 10% reduction in the odds of asthma-related ER visits or hospitalisations.³⁶ Therefore, ongoing efforts to enhance medication adherence are essential to reduce its economic impact on patients with asthma. In the USA, several state governments have implemented laws which cap the cost of asthma inhalers for patients at between \$25 and \$50 starting in 2025,³⁷ while some pharmaceutical manufacturers have introduced caps on out-of-pocket spending for asthma inhalers for certain patients.³⁸

There are several strengths of this study. First, our study was conducted with a nationally representative survey dataset, which enhanced our generalisability to the overall US population. Furthermore, by using data from 2011 to 2022, we provided a comprehensive view of the trend and prevalence in CRN among US adults with asthma over the past 12 years, as well observations of public policy that expanded health insurance access during that time. However, there are some limitations to our study. First, the NHIS relies on self-reporting by respondents, and recall bias might exist. Without medical records or diagnostic tests, individuals' disease status might be misclassified. Future research using data sources that can be linked to clinical healthcare records may mitigate disease misclassification. Second, due to the cross-sectional design, the results can only be interpreted as associations rather than causal relationships. Third, we were unable to evaluate the effect of asthma severity due to limited measures in the NHIS. It is possible that the severity of asthma might affect a patient's financial determinants of health, and in turn lead to impacts on CRN. Fourth, due to limited measures in the NHIS, we could not include variables reflecting economic indicators, such as the consumer price index.³⁹ Future studies may consider adjusting for factors that account for changes in medication prices when assessing CRN. Fifth, as joinpoint regression analysis was primarily designed to evaluate the direction of trends,¹⁶ we could not control for covariates in the trend analysis. Therefore, further validation using different methods for trend analysis is necessary to avoid potential overestimations or underestimations of trends in CRN. Sixth, questions regarding CRN in the NHIS were broad and based on the overall medications taken by respondents. It is possible that the cost of asthma medication might not be the driver for CRN, but rather a costlier non-asthma comorbidity. However, we adjusted for the number of comorbidities to account for the effects of non-asthma medications. Further investigation into CRN specific to asthma medications is required. Finally, NHIS questions about CRN did not specify whether respondents with CRN shared or took other's medications to overcome their cost constraints.⁴⁰ Patients engaging in such behaviours might still have good asthma control due to continued medication use,⁴⁰ which could potentially underestimate the impact of CRN on asthma control.

In conclusion, we observed a declining trend in the prevalence of CRN over the past 12 years, during which time nearly one in six US adults with asthma was non-adherent to medications due to costs. Several factors, including demographics and comorbidities, were found to be determinants of CRN. Patients with asthma who had CRN were at an elevated risk of experiencing asthma-related adverse events. Since asthma is one of the leading chronic diseases, the burden in cost-related non-adherence to medications highlights the need for appropriate policies and social support to address such problems.

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REFERENCES

- Global Initiative for Asthma. Global strategy for asthma management and prevention, 2023. 2023. Available: www.ginasthma.org
- Nurmamagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008–2013. *Ann Am Thorac Soc* 2018;15:348–56.
- Duan KI, Birger M, Au DH, et al. Health Care Spending on Respiratory Diseases in the United States, 1996–2016. *Am J Respir Crit Care Med* 2023;207:183–92.
- Engelkes M, Janssens HM, de Jongste JC, et al. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J* 2015;45:396–407.
- Barnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care* 2015;60:455–68.
- Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol* 2006;118:899–904.
- Bidwal M, Lor K, Yu J, et al. Evaluation of asthma medication adherence rates and strategies to improve adherence in the underserved population at a Federally Qualified Health Center. *Res Soc Adm Pharm* 2017;13:759–66.
- Cardet JC, Chang K-L, Rooks BJ, et al. Socioeconomic status associates with worse asthma morbidity among Black and Latinx adults. *J Allergy Clin Immunol* 2022;150:841–9.
- Kang H, Lobo JM, Kim S, et al. Cost-related medication non-adherence among U.S. adults with diabetes. *Diabetes Res Clin Pract* 2018;143:24–33.
- Khera R, Valero-Elizondo J, Das SR, et al. Cost-Related Medication Nonadherence in Adults With Atherosclerotic Cardiovascular Disease in the United States, 2013 to 2017. *Circulation* 2019;140:2067–75.
- Lago-Hernandez C, Nguyen NH, Khera R, et al. Cost-Related Nonadherence to Medications Among US Adults With Chronic Liver Diseases. *Mayo Clin Proc* 2021;96:2639–50.
- Shi L, Li T, Luck J, et al. The Association of Medicaid expansion with prescription drug utilization and expenditure among low-income participants with asthma. *J Asthma* 2023;60:2030–9.
- National health interview survey, 2022 survey description: national center for health statistics. 2023. Available: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2022/srtydesc-508.pdf
- Pate CA, Zahran HS, Qin X, et al. Asthma Surveillance – United States, 2006–2018. *MMWR Surveill Summ* 2021;70:1–32.
- Xia T, Qiu H, Yu B, et al. Cost-related medication nonadherence in US adults with asthma: The National Health Interview Survey, 2013–2020. *Ann Allergy Asthma Immunol* 2023;131:606–13.
- Liu B, Kim H-J, Feuer EJ, et al. Joinpoint Regression Methods of Aggregate Outcomes for Complex Survey Data. *J Surv Stat Methodol* 2023;11:967–89.
- National Cancer Institute, National Institutes of Health. Joinpoint regression program. 2023. Available: <https://surveillance.cancer.gov/joinpoint/>
- Suri R, Macinko J, Inkelas M, et al. The Relationship Between Insurance Status and the Affordable Care Act on Asthma Outcomes Among Low-Income US Adults. *Chest* 2022;161:1465–74.
- Wang J, Zhang X, Zhang L, et al. Age-Related Clinical Characteristics, Inflammatory Features, Phenotypes, and Treatment Response in Asthma. *J Allergy Clin Immunol Pract* 2023;11:210–9.
- Cohen RA, Zammitti EP. High-deductible Health Plan Enrollment Among Adults Aged 18–64 With Employment-based Insurance Coverage. *NCHS Data Brief* 2018;1–8.
- Rastas C, Bunker D, Gampa V, et al. Association Between High Deductible Health Plans and Cost-Related Non-adherence to Medications Among Americans with Diabetes: an Observational Study. *J Gen Intern Med* 2022;37:1910–6.
- Lee H, Park JH, Floyd JS, et al. Combined Effect of Income and Medication Adherence on Mortality in Newly Treated Hypertension: Nationwide Study of 16 Million Person-Years. *J Am Heart Assoc* 2019;8:e013148.
- Martinez ME, Ward BW. Health Care Access and Utilization Among Adults Aged 18–64, by Poverty Level: United States, 2013–2015. *NCHS Data Brief* 2016;1–8.
- Blavin F, Karpman M, Kenney GM, et al. Medicaid Versus Marketplace Coverage For Near-Poor Adults: Effects On Out-Of-Pocket Spending And Coverage. *Health Aff (Millwood)* 2018;37:299–307.
- Camargo CA Jr, Rane PB, Beck AF, et al. Geographic variation in disease burden among patients with severe persistent asthma in the United States. *Ann Allergy Asthma Immunol* 2024;132:602–9.
- Miller CE, Vasan RS. The southern rural health and mortality penalty: A review of regional health inequities in the United States. *Soc Sci Med* 2021;268:113443.
- Poureslami I, FitzGerald JM, Tregobov N, et al. Health literacy in asthma and chronic obstructive pulmonary disease (COPD) care: a narrative review and future directions. *Respir Res* 2022;23:361.
- Al-Mansouri A, Hamad AI, Al-Ali FS, et al. Pill-burden and its association with treatment burden among patients with advanced stages of chronic kidney disease. *Saudi Pharm J* 2023;31:678–86.
- Kini V, Ho PM. Interventions to Improve Medication Adherence: A Review. *JAMA* 2018;320:2461–73.
- Williams LK, Peterson EL, Wells K, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol* 2011;128:1185–91.
- Murphy AC, Proeschal A, Brightling CE, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax* 2012;67:751–3.
- Dusetzina SB, Besaw RJ, Whitmore CC, et al. Cost-Related Medication Nonadherence and Desire for Medication Cost Information Among Adults Aged 65 Years and Older in the US in 2022. *JAMA Netw Open* 2023;6:e2314211.
- Wilson SR, Strub P, Buist AS, et al. Shared Treatment Decision Making Improves Adherence and Outcomes in Poorly Controlled Asthma. *Am J Respir Crit Care Med* 2010;181:566–77.
- Desai SM, Chen AZ, Wang J, et al. Effects of Real-time Prescription Benefit Recommendations on Patient Out-of-Pocket Costs: A Cluster Randomized Clinical Trial. *JAMA Intern Med* 2022;182:1129–37.
- Bender BG, Rand C. Medication non-adherence and asthma treatment cost. *Curr Opin Allergy Clin Immunol* 2004;4:191–5.
- Delea TE, Stanford RH, Hagiwara M, et al. Association between adherence with fixed dose combination fluticasone propionate/salmeterol on asthma outcomes and costs*. *Curr Med Res Opin* 2008;24:3435–42.
- American Lung Association. Improving access to affordable inhalers. Available: <https://www.lung.org/blog/affordable-inhalers> [Accessed 11 Jun 2024].
- Allergy & Asthma Network. Drug companies step forward with voluntary price caps on inhalers. Available: <https://allergyasthmanetwork.org/news/drug-company-asthma-inhaler-price-cap/> [Accessed 02 Jun 2024].
- Yang EJ, Galan E, Thombley R, et al. Changes in Drug List Prices and Amounts Paid by Patients and Insurers. *JAMA Netw Open* 2020;3:e2028510.
- Dawson S, Johnson H, Huntley AL, et al. Understanding non-recreational prescription medication-sharing behaviours: a systematic review. *Br J Gen Pract* 2024;74:e183–8.

ARTIGO ORIGINAL

Associação entre privação socioeconômica, etnia e resultados de saúde em crianças em idade pré-escolar com sibilância recorrente na Inglaterra: um estudo de coorte retrospectivo

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RESUMO

Contexto: Crianças em idade pré-escolar apresentam uma das maiores cargas de sibilância aguda. Foram investigadas diferenças no uso de cuidados de saúde, tratamentos e resultados para sibilância recorrente/asma em pré-escolares de diferentes contextos étnicos e socioeconômicos.

Métodos: Estudo de coorte retrospectivo utilizando dados do Clinical Practice Research Datalink vinculados às Estatísticas de Episódios Hospitalares na Inglaterra. Foram reportados o número de apresentações agudas e hospitalizações, estratificados pelo índice de múltipla privação (IMD) e etnia; e fatores associados à não escalada do tratamento e taxas de hospitalização, utilizando modelos de regressão logística multivariada e de Poisson.

Resultados: Foram incluídas 194.291 crianças em idade pré-escolar. Entre as crianças que não receberam medicamentos preventivos para asma, aquelas do quintil mais privado de IMD (OR ajustado 1,67; IC 95% 1,53 a 1,83) e as crianças sul-asiáticas (1,77; 1,64 a 1,91) tiveram maior probabilidade de uso elevado de medicamentos de alívio. Onde não ocorreu encaminhamento para especialistas, as chances de encaminhamento foram maiores no quintil mais privado (1,39; 1,28 a 1,52) e em crianças sul-asiáticas (1,86; 1,72 a 2,01) em comparação ao quintil menos privado e crianças brancas, respectivamente.

As taxas de hospitalização por sibilância/asma foram significativamente maiores em crianças do quintil mais privado (IRR ajustado 1,20; IC 95% 1,13 a 1,27) em comparação ao menos privado e em crianças sul-asiáticas (1,57; 1,44 a 1,70) e negras (1,32; 1,22 a 1,42) em comparação às crianças brancas.

Conclusões: Foram identificadas desigualdades no tratamento e morbidade por sibilância/asma em crianças em idade pré-escolar de contextos mais privados e não brancos. É necessária uma abordagem multifacetada para combater as desigualdades de saúde tanto a nível nacional quanto local, incluindo uma abordagem mais integrada e padronizada ao tratamento, a fim de melhorar os resultados de saúde em crianças com sibilância/asma pré-escolar.

INTRODUCTION

Wheezing illnesses in young children are extremely common, with up to half experiencing an episode by the age of 6 years.^{1,2} Most episodes are mild, but some children will experience persistent or frequent symptoms resulting in multiple emergency healthcare attendances, and poor quality of life.^{3,4} The prevalence of preschool children presenting acutely with wheeze is already higher than in any other age group and increasing.^{5,6} Although not every preschool child who wheezes has asthma, many will go on to be diagnosed with asthma in later childhood.^{6,7}

The decision to initiate effective regular treatments to prevent asthma attacks, including inhaled corticosteroids,^{8,9} should ideally follow a

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- In adults and older children with asthma, there is evidence of inequality in treatment, healthcare utilisation and burden of illness between different ethnic and socioeconomic groups.
- We do not know if similar differences in wheeze/asthma-related health outcomes exist in preschool children.

WHAT THIS STUDY ADDS

- This is the first study to explore the impact of socioeconomic and ethnic factors on the severity and frequency of wheezing illnesses in preschool children.
- We have identified inequalities in the treatment and morbidity experienced by preschool children with wheeze/asthma from more deprived socioeconomic and from non-White ethnic backgrounds.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- National initiatives and strategies to reduce health inequalities and improve health outcomes in people with asthma and wheeze should include a focus on preschool children and consider the additional resources that are needed specifically for this age group and their families.

confirmed physician diagnosis of asthma. However, objective lung function testing is not practical in very young children, and the sheer volume of preschool wheezing illnesses seen by clinicians, many of which will be self-limiting viral respiratory infections, means clinicians are often hesitant to label preschool children, even those with frequent wheezing, as having asthma.¹⁰ This has resulted in overreliance on ad hoc symptomatic treatment with short-acting relievers (ie, short-acting beta-2 agonists (SABAs)) and short courses of oral corticosteroids (OCS).

Recent guidance, therefore, recommends that health professionals should base decisions to treat preschool children with maintenance preventer medications on the severity and frequency of wheeze episodes, and not necessarily on confirming an asthma diagnosis.¹¹

In older children and adults with asthma, treatment approaches, healthcare use and burden of illness vary between different ethnic and socioeconomic groups.^{12–14} The majority of previous studies have been in adults, and the limited data available for children have predominantly been from survey-based studies reliant on patient recall.^{15–17} In the UK, addressing the impact of poverty, and ethnicity on asthma outcomes has been identified as a research¹⁸ and health policy¹⁹ priority.

We aimed to improve understanding of the burden of wheezing illnesses in preschool children, regardless of an ‘asthma’ diagnosis, by exploring whether healthcare use and treatment decisions for preschool wheeze differ between children from different socioeconomic and ethnic backgrounds, and to describe factors associated with worse clinical outcomes.

By finding groups of young children with the highest frequency of wheeze episodes, and those where treatment and/or referrals for specialist care are not initiated despite a high burden of illness, future health policies and interventions to improve management of recurrent preschool wheeze can be designed to target at-risk groups.

METHODS

Data source

For this retrospective cohort study, we used routinely collected healthcare data from the Clinical Practice Research Datalink (CPRD) Aurum national primary care database, containing deidentified patient information from consenting general practices (GPs). As of 2022, the dataset included over 13 million currently registered patients²⁰ and is broadly representative of the UK population in terms of age, gender and ethnicity.²¹ CPRD contains detailed coded data on patient demographics, diagnoses, prescription records, laboratory tests and hospital referrals. Primary care data from the May 2022 build²⁰ were linked via patient residential postcode to small-area-level data²² for socioeconomic deprivation measures, and rural–urban classification data.²³ Linkage to secondary care data was available from NHS England’s Hospital Episode Statistics (HES) Admitted Patient Care (APC),²⁴ Outpatient (OP)²⁵ and Accident and Emergency (A&E)²⁶ databases.

Population

The study population was derived from children aged under 5 years old, registered with GPs in England contributing data to CPRD Aurum who were eligible for linkage with HES.

Children born in a 5-year timeframe (1 January 2009 to 31 December 2013 inclusive), presenting to primary or secondary care with at least one episode of wheeze before their fifth birthday were potentially eligible for inclusion. A wheeze event was defined by the presence of a wheeze or asthma clinical diagnostic code, or prescription data for wheeze/asthma medications from primary care records, or a visit to the A&E department and/or hospital for treatment of asthma/wheeze (based on ICD10 and A&E codes).

We excluded children with a coded diagnosis of primary ciliary dyskinesia, cystic fibrosis, bronchopulmonary dysplasia, bronchiolitis obliterans, interstitial lung disease or bronchiectasis.

Outcomes

Children fulfilling the inclusion criteria had their electronic records searched for further acute wheeze/asthma-related episodes, medication prescriptions and hospital attendances/admissions from birth until their sixth birthday. Follow-up until the sixth birthday was to allow for at least 1 year of follow-up in children presenting for the first time near their fifth birthday. Only children with complete CPRD records until their sixth birthday were included. The 5-year recruitment period was chosen to allow for a child to be followed up until their sixth birthday (potentially up to 31 December 2019) without overlapping with the start of the COVID national lockdown measures in 2020.

Acute attendances to primary or secondary care were defined using clinical diagnostic ‘medcodes’ for primary care, and ICD10/A&E wheeze/asthma codes for secondary care. Medication codes were used to determine prescriptions for asthma relievers (ie, SABAs) and preventers (inhaled steroids, long-acting beta-2 ago-

nists and leukotriene receptor antagonists) from primary care records. A secondary care referral was defined by the presence of a paediatric clinic appointment at any point during follow-up using HES outpatient activity data.

To explore factors associated with non-referral to secondary care in children where a referral was potentially indicated, we agreed on a threshold to define ‘referral indicated’ based on the previous burden of illness:

1. More than five reliever prescriptions AND either (a) >2 A&E attendances, (b) >1 hospital admission or (c) >2 courses of OCS OR
2. More than 10 reliever prescriptions OR
3. More than 5 OCS prescriptions OR
4. One or more critical care admissions with asthma/wheeze OR
5. More than five A&E attendances with asthma/wheeze OR
6. More than two hospital admissions with asthma/wheeze

A trial of preventer medication was defined as being indicated based on a previous prescription history of >5 reliever inhalers.

Variables

The following demographic data were extracted from CPRD and HES datasets and included in analyses: age of first wheeze, sex, region of GP, socioeconomic status, ethnicity, and urban/rural status of home address.

Socioeconomic status for each participant was based on the 2019 English Index of Multiple Deprivations (IMD) linked to the patient’s postcode, grouped into quintiles. IMD is a composite measure derived from a number of ‘domains’ covering different aspects of material deprivation including health, employment, income, education and skills, housing, crime, living environment and access to services. The overall composite index (IMD) is calculated as a weighted sum of the individual domain scores. A score of one denotes ‘least deprived’ and five denotes ‘most deprived’.²² Ethnicity was defined, from HES datasets, as the most commonly recorded ethnicity value across all healthcare episodes recorded in HES APC, outpatient and A&E datasets.

For children, CPRD provides month and year of birth only. The date of birth was, therefore, approximated as the first day of the month of birth combined with the recorded month and year of birth. The rural–urban dataset was used to categorise patient residences as either primarily ‘rural’ or ‘urban’ as a binary variable at the patient postcode level. The rural–urban classification for England is produced by the United Kingdom’s Office for National Statistics and is based on census population data.

The ‘rural’ or ‘urban’ designation is given based on the size of the resident population in a given geographical area and does not reflect the land use, policy or financial characteristics of an area. Areas are classified as rural if they fall outside of settlements with more than a 10 000-resident population.²⁷

Clinical diagnostic codes (medcode) were used to define the presence of clinical comorbidities including atopy (defined as the presence of eczema, hayfever, food allergy and/or rhinitis), gastroesophageal reflux, prematurity and history of bronchiolitis. The comorbidity was classified as being present (or absent) based on the presence (or not) of the relevant code at any point during follow-up.

Statistical analyses

Baseline characteristics of the cohort were presented by sex, region of GP, urban/rural classification, IMD and ethnicity. The age of first presentation with wheeze/asthma, number of healthcare attendances, hospital admissions and reliever prescriptions was summarised as: mean (SD) or median (IQR) for continuous variables as appropriate, and as counts and percentages for categorical and binary variables.

Healthcare use was explored comparing differences in the number of children with >1 acute wheeze/asthma presentations to either GP or A&E by socioeconomic and ethnic group using the χ^2 test. Differences in the mean percentage of acute attendances to primary care (as a proportion of all presentations to either primary or secondary care) were compared between different socioeconomic and ethnic groups using the analysis of variance (ANOVA) test.

Poisson regression analyses were performed to determine factors associated with higher rates of (1) hospital admissions, (2) acute

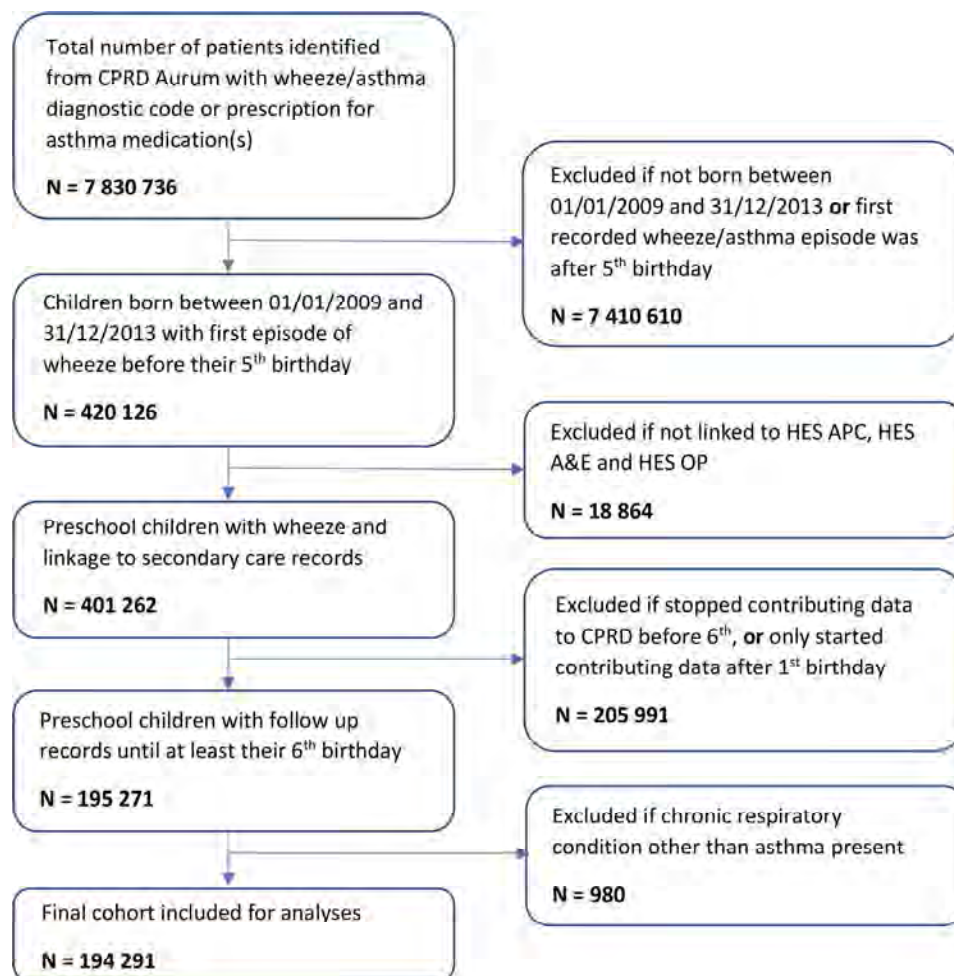


Figure 1 Flow diagram of study population. A&E, accident and emergency; APC, admitted patient care; CPRD, clinical practice research datalink; HES, hospital episode statistics; OP, outpatients.

healthcare attendances and (3) relievers prescribed for preschool wheeze/asthma during the first 6 years of life, adjusted for available clinical and demographic characteristics. Robust SEs were used to control for mild violations of underlying model assumptions.

Factors associated with treatment escalation were described using the number of relievers prescribed (as a surrogate marker for duration/severity of symptoms) before the first trial of a preventer medication reported by socioeconomic status and ethnicity.

Separate multiple logistic regression analyses were performed in children never trialled on a preventer medication, and in those never referred to secondary care, to identify factors associated with poor symptomatic control in children where treatment had not been escalated. We restricted the logistic regression analyses to children in whom a referral was 'never made' because it was not possible to accurately determine the reason for referral (in children who were referred to secondary care) from the data available, that is, whether for wheeze/asthma or an unrelated condition. Similarly, we only included children 'never trialled' on a preventer medication to allow for methodological consistency between logistic regression models. Second, children trialled on preventer medications were not homogeneous in terms of the number of relievers prescribed prior to their first preventer trial.

The dependent (response) variable for each logistic regression model was, therefore, (1) whether a trial of preventer was indicated or not and (2) whether referral was indicated or not as dichotomous variables based on criteria detailed earlier.

All models were adjusted using the covariates listed earlier. Statistical significance was set at $p < 0.05$. All analyses were performed using STATA statistical software, V.17.

Patient and public involvement

Two patient and public involvement (PPI) members identified through the Generation R alliance with experience of caring for a

child with recurrent preschool wheeze were part of the project steering committee. They have commented on the study protocol and have been consulted on the contextual interpretation of the study findings and dissemination strategies.

RESULTS

Baseline characteristics

The cohort consisted of 194 291 children (figure 1). The majority were male (57%), lived in an urban area (87%) and were from a white ethnic background (75%). Regions in England contributing the most children to the cohort were the North-West, West Midlands, London and South-East. Median age of presentation with the first episode of wheeze/asthma (not including bronchiolitis) was 1.0 (IQR 0.0–2.0) years. Almost half (46%) the cohort had evidence of atopy (table 1).

Healthcare use

The majority of preschool children had one or no A&E attendance with acute wheeze/asthma in the first 6 years of life. For each increasing deprivation quintile, there was an increasing proportion of children with >1 A&E attendances. The proportion of children from IMD quintile 5 with >1 A&E attendances was 1.6 times greater compared with children from IMD quintile 1 (3.1% vs 1.9%, $p < 0.001$). Similarly, a larger proportion of children from the most deprived quintile had >1 primary care attendances with acute wheeze/asthma compared with children from the least, however the difference was much smaller (14.6% vs 14.1%, $p = 0.025$) (figure 2A).

White children had the lowest proportion of >1 A&E or GP attendances with acute wheeze/asthma compared with any other ethnic background. By comparison, black children had more than double the proportion of >1 A&E attendances (4.6% vs 2.2%, $p < 0.001$), and South Asian children had 1.4 times the proportion of >1 acute GP attendances (18.9% vs 13.8%, $p < 0.001$) (figure 2B).

Table 1 Baseline characteristics of cohort and healthcare utilisation during follow-up

	Total N=1 94 291
Sex	
Female	84 122 (43%)
Male	110 169 (57%)
Region of registered practice	
North East	5518 (3%)
North West	38 545 (20%)
Yorkshire and Humber	5929 (3%)
East Midlands	2980 (2%)
West Midlands	31 850 (16%)
East of England	8713 (4%)
London	36 135 (19%)
South East	40 472 (21%)
South West	19 937 (10%)
Missing/unknown	4212 (2%)
Urban or rural classification of household	
Urban	168 532 (87%)
Rural	25 619 (13%)
Missing/unknown	140 (0.1%)
2019 English IMD quintiles (1=least deprived)	
1	37 345 (19%)
2	34 610 (18%)
3	34 783 (18%)
4	40 194 (21%)
5	47 219 (24%)
Missing/unknown	140 (0.1%)
Recorded ethnicity	
White	146 408 (75%)
South Asian	18 834 (10%)
Black	9248 (5%)
Other	4635 (2%)
Mixed	7723 (4%)
Missing/unknown	7443 (4%)
Clinical history	
History of atopy (eczema/rhinitis/hayfever/allergy)	88 440 (46%)
History of bronchiolitis	25 797 (13%)
History of GORD	16 082 (8%)
History of premature birth	8363 (4%)
Median (IQR) age of first wheeze episode in years	1.0 (0.0–2.0)
Healthcare utilisation during follow-up	
Median (IQR) number of acute GP attendances*	0.0 (0.0–1.0)
Median (IQR) number of A&E attendances*	0.0 (0.0–0.0)
Median (IQR) number of hospital admissions*	0.0 (0.0–0.0)
Median (IQR) number of relievers prescribed	2.0 (1.0–4.0)

*Refers to healthcare use for acute episodes of wheeze or asthma only.
A&E, accident and emergency; GORD, gastro-oesophageal reflux disease; GP, general practice; IMD, index of multiple deprivation.

As a proportion of healthcare attendances to either primary or secondary care with acute wheeze/asthma, the majority of presentations were to primary care. For each increasing deprivation quintile, the proportion of presentations to A&E increased (from 12.7% in the least to 18.2% in the most deprived). A one-way ANOVA was performed to compare the effect of ethnicity on the proportion of acute presentations to GP versus A&E. Black children had the highest proportion of acute presentations to A&E (24.3%) and white

children the least (15.1%) ($p<0.0001$) (online supplemental table S1).

Adjusted associations between characteristics and rates of preschool wheeze-related hospital admissions

Increasing deprivation was associated with higher rates of hospitalisations. Compared with children from the least deprived quintile 1, children from quintile 2 had 5% (adjusted IRR 1.05; 95% CI 1.00 to 1.10), quintile 3 had 13% (1.13; 1.08 to 1.19), quintile 4 had 17% (1.17; 1.11 to 1.23) and quintile 5 had 20% (1.20; 1.13 to 1.27) higher rates of acute hospital admissions with wheeze/asthma.

Compared with white preschool children, those from South Asian (adjusted IRR 1.57; 95% CI 1.44 to 1.70), black (1.32; 1.22 to 1.42), other (1.21; 1.10 to 1.32) and mixed (1.25; 1.16 to 1.34) ethnic backgrounds all had higher rates of acute hospital admissions with wheeze/asthma (figure 3).

Geographically, compared with children living in the North East of England, the rate of hospital admissions for wheeze/asthma were approximately 30% lower in children living in the East Midlands (adjusted IRR 0.71; 0.61 to 0.82), East of England (0.70; 0.63 to 0.79) and London (0.73; 0.67 to 0.80), 16% lower in children living in Yorkshire and Humber (0.84; 0.74 to 0.95) and 10% lower in children living in the South East of England (0.90; 0.82 to 0.98).

In terms of clinical predictors, children with a history of bronchiolitis had almost double the rate of hospital admissions (adjusted IRR 1.97; 1.89 to 2.04), compared with children without a history of bronchiolitis, whereas children with a history of atopy had 67% (1.67; 1.61 to 1.73), Gastro-oesophageal reflux disease had 6% (1.06; 1.01 to 1.11), and being born prematurely had 37% (1.37; 1.28 to 1.46) higher rates of wheeze-related hospitalisations (figure 3).

Additional Poisson analyses were performed to explore factors associated with increasing rates of acute presentations to GP or A&E (online supplemental table S2) and prescriptions of reliever medications (online supplemental table S3), which demonstrated similar associated factors as those for hospital admission rates.

Escalation of treatment—trial of preventer medication

A higher proportion of children from increasing deprivation quintiles were prescribed ≥ 10 relievers prior to a trial of preventer (from 1.6% in the least to 3.5% in the most deprived) (online supplemental table S4), and almost double the proportion of South Asian (5.2%) and black (4.3%) children received ≥ 10 reliever prescriptions prior to a trial of preventer medication compared with children from white (2.1%), other (2.5%) or Mixed (2.6%) ethnic backgrounds (online supplemental table S5).

Of those children not trialled on preventer medication ($n=1\ 28\ 351$), when adjusted for IMD, ethnicity, sex, urbanicity, region and clinical characteristics, children from the most deprived background were more likely to have an indication for preventer medication compared with children from the most affluent background (OR 1.67; 95% CI 1.53 to 1.83). Compared with white children, South Asian (1.77; 1.64 to 1.91) and black (1.43; 1.28 to 1.60) children were also at higher risk of having an indication for preventer medication, despite this not being trialled.

Male sex (OR 1.24; 1.17 to 1.31), a rural postcode (OR 1.22; 1.12 to 1.33), living in the East Midlands (OR 1.30; 1.03 to 1.64) or West Midlands (OR 1.19; 1.01 to 1.39) of England, and the presence/history of atopy (OR 1.51; 1.43 to 1.59) or bronchiolitis (OR 1.64; 1.53 to 1.75) or premature birth (OR 1.25; 1.11 to 1.41) or younger age of first wheeze presentation (OR 0.72; 0.70 to 0.74) were all found to be associated with non-escalation of treatment despite indication based on number of reliever prescriptions (figure 4).

Escalation of treatment—referral to secondary care

In children where referral to secondary care had not occurred ($n=1\ 03\ 491$), the risk of indication was 40% higher in children from the most deprived background, than children from the most affluent background (adjusted OR 1.39; 95% CI 1.28 to 1.52) and almost 90% higher in South Asian than white children (1.86; 1.72 to 2.01).

Other factors found to be significantly associated with indication despite non-referral were male sex (adjusted OR 1.37; 1.29 to 1.44),

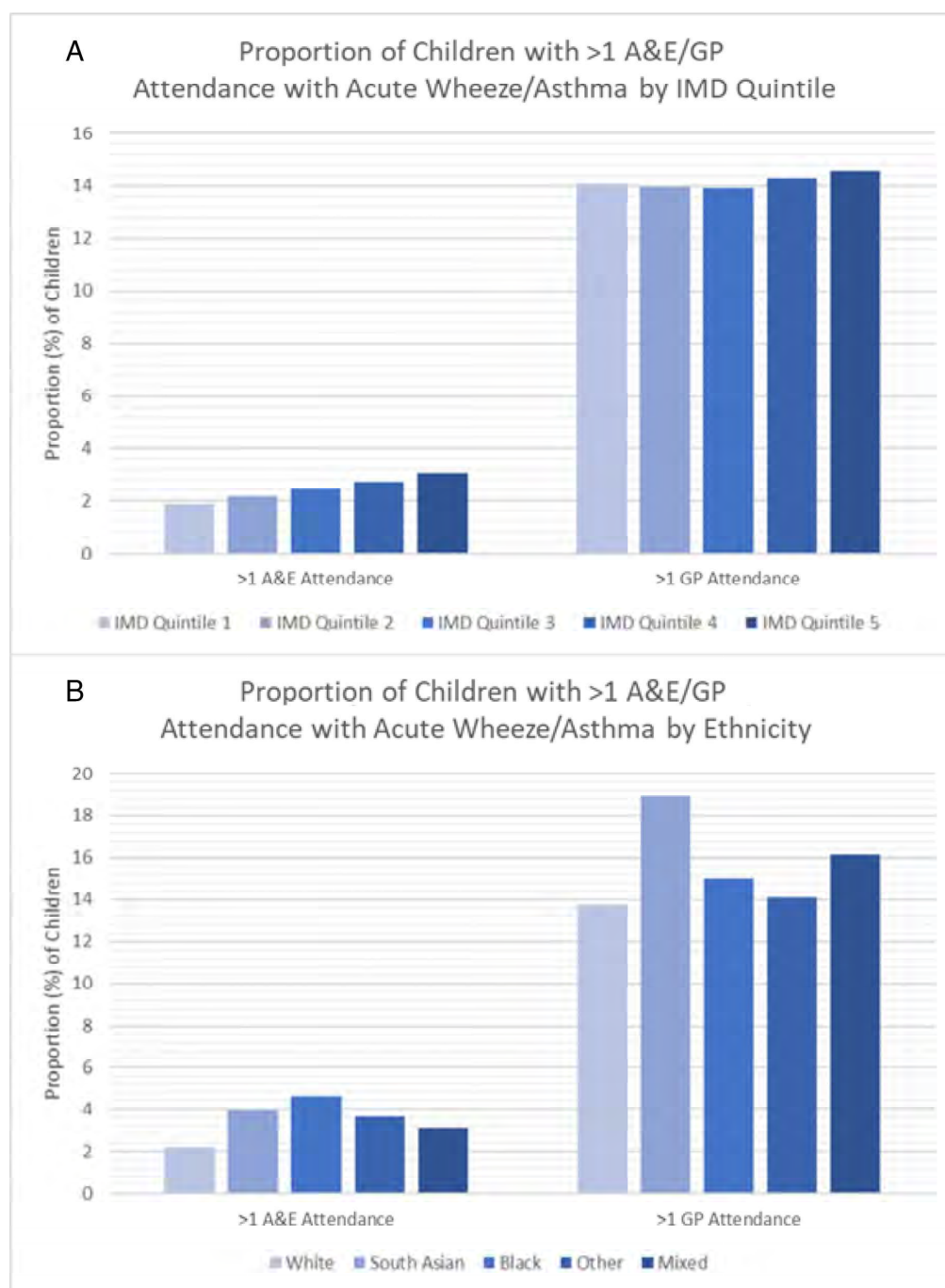


Figure 2 Bar graphs to show the proportion (%) of children in our cohort with more than one accident and emergency (A&E) or general practice (GP) attendance with an acute wheeze or asthma episode by index of multiple deprivation (IMD) quintile (A) and by ethnicity (B).

a rural postcode (1.14; 1.05 to 1.24) and a history of atopy (1.91; 1.81 to 2.01), bronchiolitis (1.59; 1.49 to 1.70) or younger age of first wheeze presentation (OR 0.75; 0.73 to 0.77). Compared with living in the North East of England, living in the North West (1.73; 1.39 to 2.14), the East Midlands (1.45; 1.08 to 1.93), the West Midlands (1.56; 1.26 to 1.94), the East of England (1.32; 1.03 to 1.68), the South East (1.49; 1.20 to 1.85) and the South West (1.68; 1.35 to 2.10) were all significantly associated with an indication for hospital referral (figure 5).

DISCUSSION

In this large retrospective cohort study of just under 200 000 preschool children, we observed significant differences in burden of illness, healthcare use, risk of acute wheeze attacks and escalation of treatment for wheeze/asthma between children from different socioeconomic and ethnic backgrounds.

Preschool children from more deprived socioeconomic, and those from South Asian and black ethnic backgrounds presented

more frequently to healthcare with acute attacks of wheeze/asthma and had higher rates of hospital admissions compared with children from less deprived socioeconomic and those from White ethnic backgrounds, even after correcting for clinical and demographic covariates.

Worryingly, these same groups of children were also less likely to be commenced on a trial of asthma preventer medication and/or referred to a hospital specialist despite this being warranted based on their burden of illness.

Comparison with other studies

Deprivation has consistently been shown to be associated with poorer asthma outcomes and more frequent attacks in adults^{28–30} and school-aged children.^{14 31 32}

A recent systematic review, which included 61 mostly adult studies comprising over 1 million patients (median age 27.9 years), found that more deprived socioeconomic status was associated with increased asthma-related A&E attendances (OR 1.61, 95% CI 1.40 to

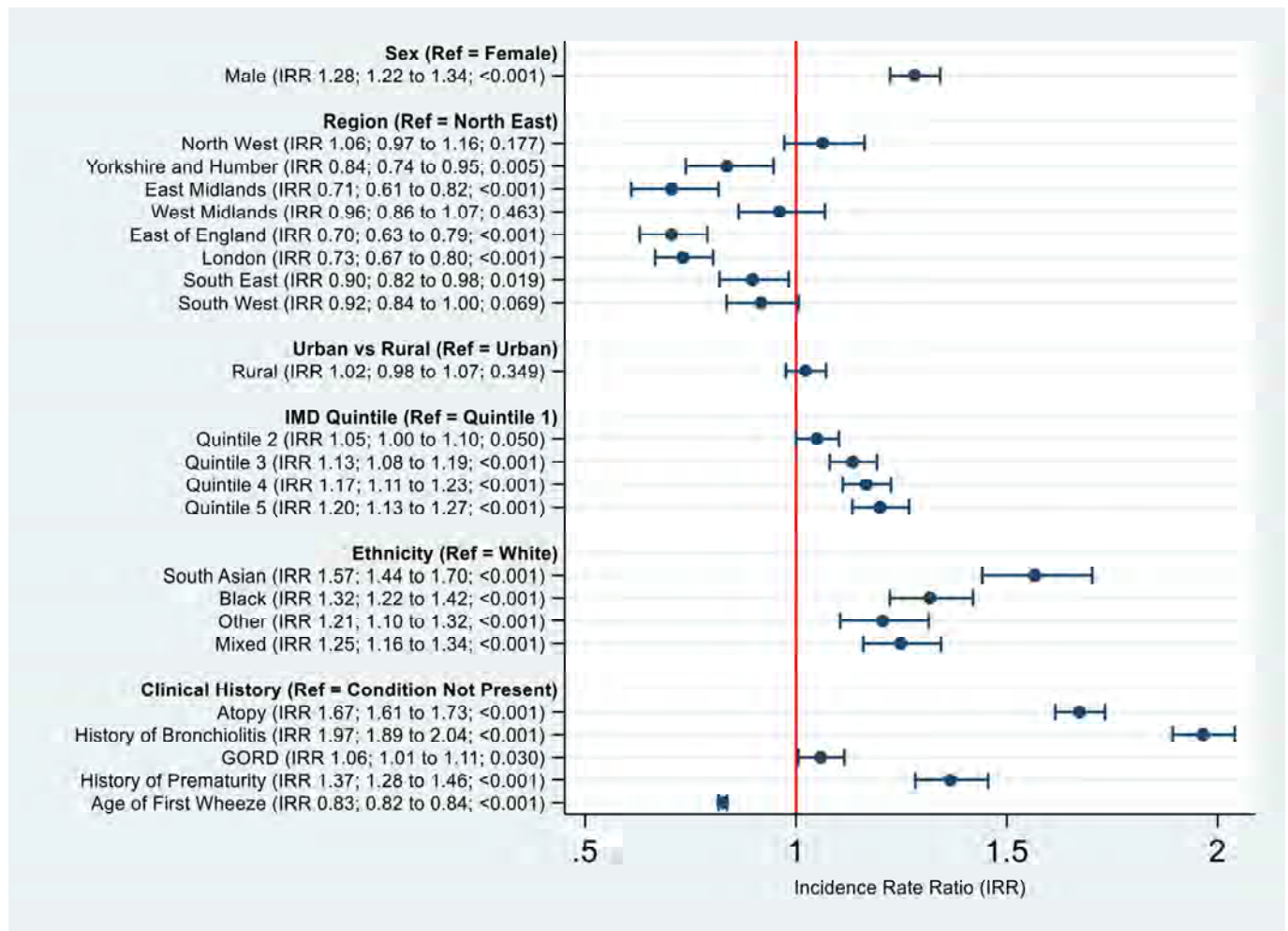


Figure 3 Poisson regression model showing incidence rate ratio for hospital admissions for preschool wheeze adjusted for all included covariates (n = 182,626). Forest plot of output from Poisson regression analysis, adjusted for all covariates presented. The incidence rate ratio (IRR) is presented adjacent to each variable, followed by the 95% CI and p-value. GORD, gastro-oesophageal reflux disease; IMD, index of multiple deprivation; Ref, reference variable.

1.84), hospitalisations (OR 1.63, 95% CI 1.34 to 1.99) and need for critical care (OR 1.76, 95% CI 1.13 to 2.73).³⁰

There have been reported differences in asthma care and outcomes observed among people of different ethnicities.^{12 13 33 34} Supporting the findings from our study, these studies observed higher rate of asthma attacks in patients (mostly adults) from black and South Asian backgrounds.

Despite preschool children having the highest burden of wheeze/asthma-related illnesses presenting to healthcare,^{5 35} there have been relatively few studies exploring the impact of ethnicity or socioeconomic status in this age group. Previous studies in preschool children have focused on reporting the prevalence of a 'physician-confirmed asthma diagnosis' as the primary outcome¹⁵ and have often been based on parental survey responses^{16 17} which are limited by recall bias.

In contrast to previous studies, we chose not to use 'asthma diagnosis' as the primary outcome. In preschool children, due to symptom overlap with other self-limiting conditions and the lack of practical objective tests, confirming an asthma diagnosis is not straightforward. Recent national guidelines and strategy documents rightly recommend escalation of treatment based on a suggestive asthma history, and on the severity and frequency of symptoms.^{36 37} To our knowledge, ours is the first study to explore the impact of socioeconomic and ethnic factors on the severity and frequency of wheezing illnesses in preschool children, and their association with hospitalisation rates and treatment escalation decisions, regardless of an asthma diagnosis.

Other key strengths of our study are its large sample size, which is representative of the wider preschool population in England, and our use of routine electronic healthcare data and standardised

clinical codes for case finding and outcome definitions. Linkage to hospital discharge data further allowed us to capture episodes more accurately regardless of healthcare setting.

Limitations

Routine healthcare data are not primarily collected for research purposes. How and what information is coded is not standardised between health professionals. However, to avoid missing potential wheeze/asthma episodes, we used a broad inclusion criterion, incorporating both clinical diagnostic and prescription codes for commonly used asthma medications.

The available datasets only allowed us to capture prescriptions issued from primary care, and not prescriptions dispensed from either hospital or A&E. This likely resulted in an underestimate of prescriptions for asthma medications in children with at least one episode, resulting in a hospital attendance or admission. Conversely, prescriptions recorded in the electronic primary care records do not necessarily represent what was dispensed by pharmacies or what was used by patients, potentially over-estimating medication usage.

Although we included clinical covariates within our analyses, it was not possible to account for all possible clinical comorbidities which may have an impact on wheeze/asthma outcomes. Obesity, as a potential confounder, was not included due to poor, infrequent and inconsistent recording of children's weights and heights within electronic records.

The coding of clinical diagnoses from outpatient appointments was largely missing, so we could not be certain that outpatient appointments were for wheeze/asthma or for another unrelated clinical condition. We accounted for this in our analyses by looking

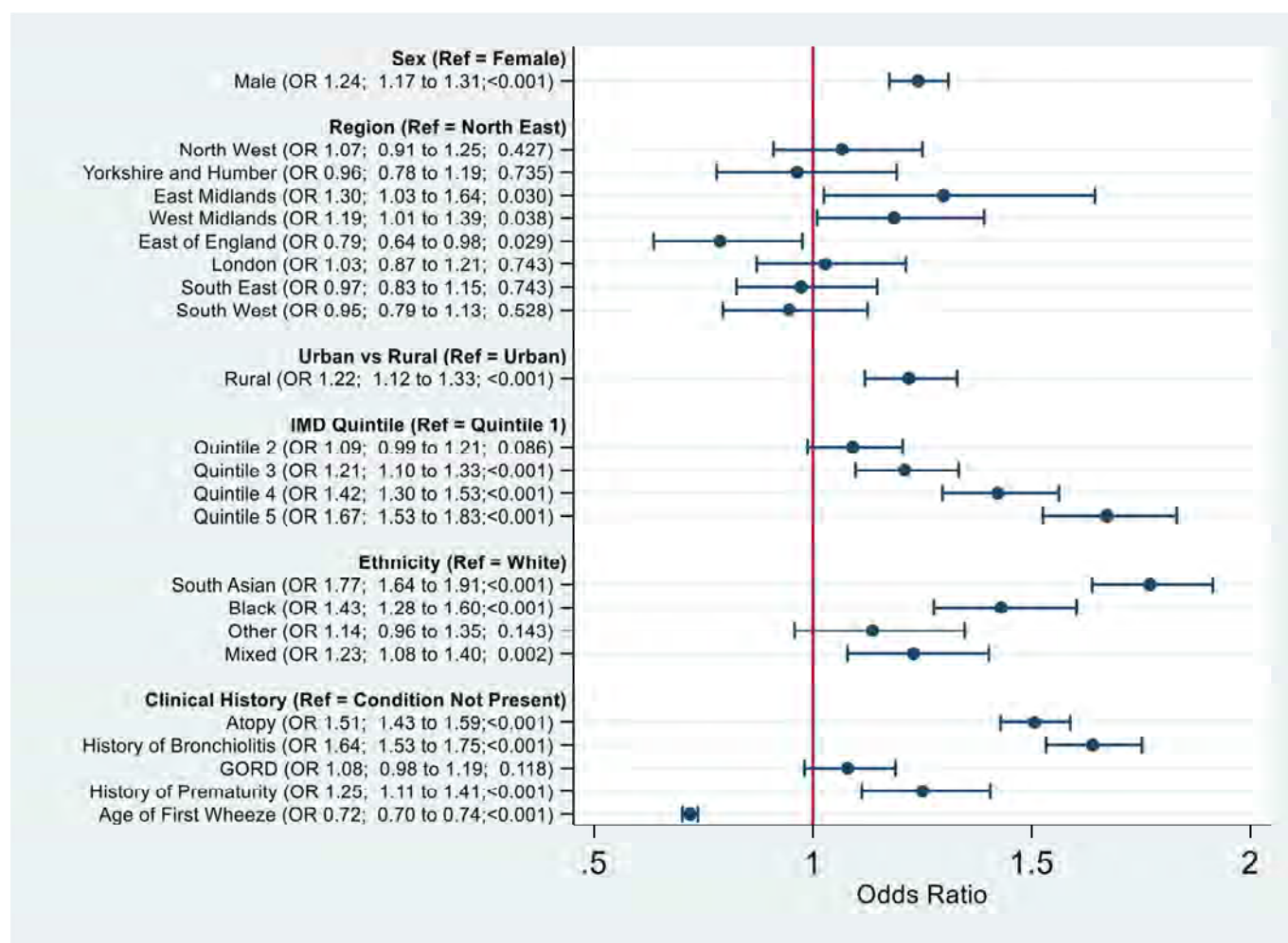


Figure 4 Multivariate logistic regression model showing odds ratio of a preventer being indicated in children not commenced on a preventer medication (n = 128,351). Forest plot of output from multivariate logistic regression analysis, adjusted for all covariates presented. The OR is presented adjacent to each variable, followed by the 95% CI and p-value. GORD, gastro-oesophageal reflux disease; IMD, index of multiple deprivation; Ref, reference variable.

specifically at 'non-referrals', as we felt we could be relatively certain that a child had not been reviewed by a hospital specialist for recurrent wheeze/asthma symptoms if there was no coded outpatient appointment on record.

Finally, due to the availability of linked secondary care data, our study cohort consisted of English preschool children only. However, as all four United Kingdom (UK) nations have access to a tax-funded universal healthcare system, our findings should be generalisable to the UK as a whole, and to other populations with similar health systems.

Implications

Reasons for variations in clinical outcomes between groups of children we observed are likely complex, multifactorial and have significant implications for the well-being of young children with recurrent episodes of wheeze. Inequalities in asthma care and outcomes have been reported in adults and older school-aged children. Initiatives to address these inequalities have been set out by national bodies,^{38,39} but key details pertaining specifically to preschool-aged children are lacking.

The measure of deprivation used in this study (2019 English IMD) is a composite measure derived from seven different domains of material deprivation, described in more detail earlier. Any initiatives to tackle deprivation and reduce health inequalities would, therefore, need to address multiple social challenges in parallel, including access to services, poverty, education and the living environment. These barriers are beyond the capabilities of individual clinicians to overcome, but require collaborative effort from all stakeholders in child health to petition for better support and funding for children at the national level.

Individually, healthcare professionals need to be cognisant that while wheezing episodes are self-limiting and mild in most preschool children, some will follow a more severe clinical course and would benefit from regular treatment and health-care follow-up.

Our PPI collaborators voiced personal experiences of challenges in conveying concerns pertaining to their children's recurrent wheeze-related illnesses to health professionals, often feeling 'not listened to' and made to feel 'like (overly) anxious parents'.

Physical and cultural barriers to accessing and delivering health-care to preschool children with recurrent wheeze need to be explored further from both families' and health professionals' perspectives. A better understanding of cultural (health beliefs, stigma and perception of chronic illness and communication barriers) and physical (accessing healthcare, continuity of care and treatment uncertainties) barriers to the delivery of care is needed to inform effective strategies and centralised policies to improve how preschool children with troublesome wheeze/asthma are cared for. These questions are currently being addressed as part of a National Institute for Health and Care Research-funded study.⁴⁰

CONCLUSIONS

Our study highlights clinically important inequalities in the treatment and morbidity experienced by a representative sample of English preschool children with wheeze/asthma from different socioeconomic and ethnic backgrounds. A multifaceted approach to tackle health inequality at both the national and local levels, which should include a more integrated and standardised approach to treatment escalation, is needed to improve health outcomes in children with preschool wheeze and asthma.

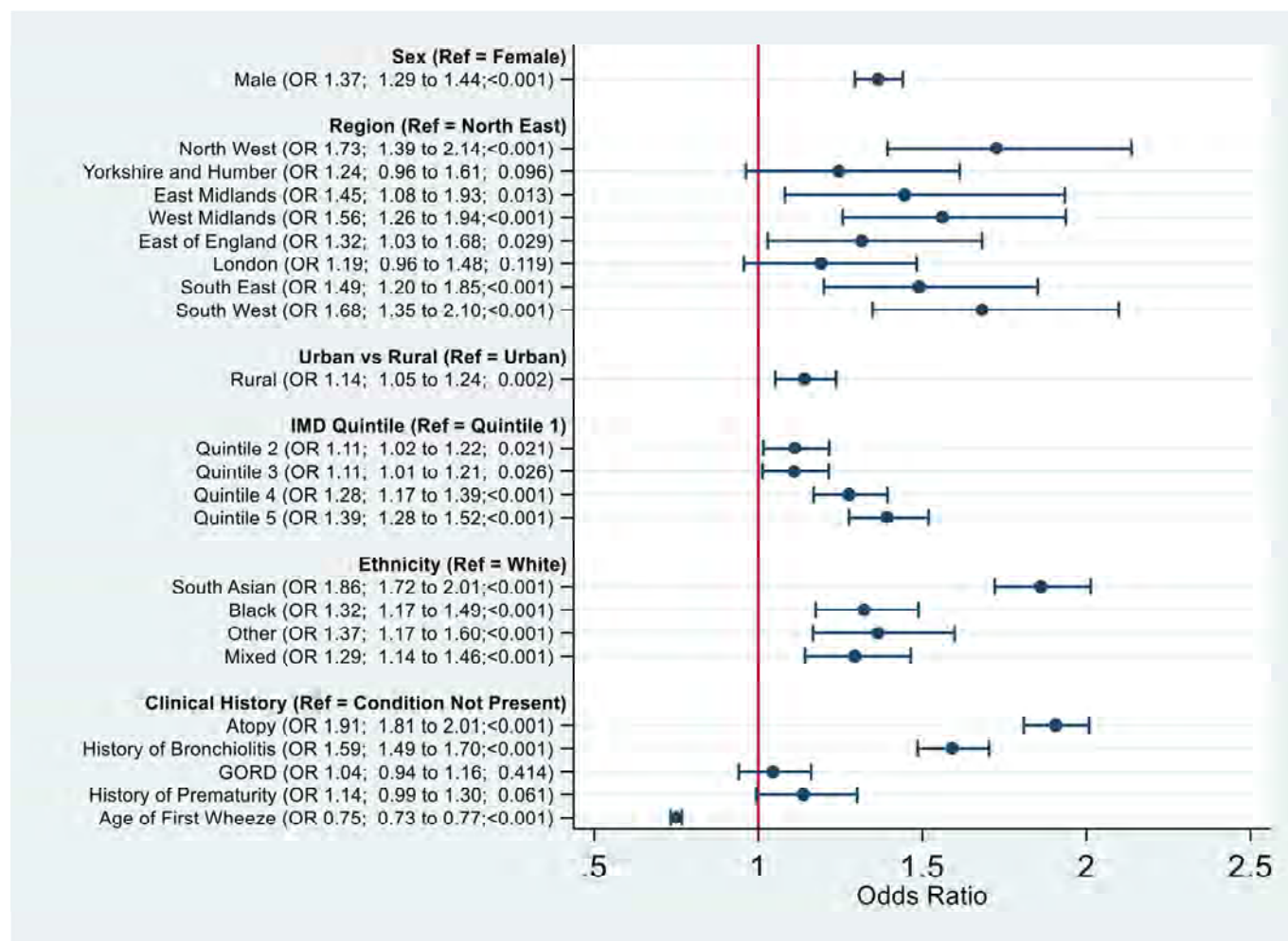


Figure 5 Multivariate logistic regression model showing odds ratio of a secondary care referral being indicated in children not referred ($n = 103$, 491). Forest plot of output from multivariate logistic regression analysis, adjusted for all covariates presented. The OR is presented adjacent to each variable, followed by the 95% CI and p-value. GORD, gastro-oesophageal reflux disease; IMD, index of multiple deprivation; Ref, reference variable.

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Contributors DL conceived the idea of the study and developed the protocol with input from CL, HP, EAG, CG and JKQ. SS extracted the data for analysis and developed the codes to identify index dates and generate birth dates. All subsequent data cleaning and analyses were conducted by DL, with support from CL, CG and JKQ. All authors interpreted the data. DL drafted and revised the manuscript, with input from all authors. The guarantor (DL) accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author (DL) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Patient consent for publication Not applicable.

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Data availability statement Data may be obtained from a third party and are not publicly available. Datasets used in this analysis were obtained via a Clinical Practice Research Datalink (CPRD) institutional licence. Requests

for data should be made directly to the CPRD via their online application portal (<https://cprd.com/research-applications>). Code lists used to identify the cohort is available at <https://github.com/dkhl1/p2am>.

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REFERENCES

- Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–8.
- Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974–80.
- Oostenbrink R, Jansingh-Piepers EM, Raat H, et al. Health-related quality of life of pre-school children with wheezing illness. *Pediatr Pulmonol* 2006;41:993–1000.
- Hafkamp-de Groen E, Mohangoo AD, Landgraf JM, et al. The impact of preschool wheezing patterns on health-related quality of life at age 4 years. *Eur Respir J* 2013;41:952–9.
- Bloom CI, Saglani S, Feary J, et al. Changing prevalence of current asthma and inhaled corticosteroid treatment in the UK: population-based cohort 2006–2016. *Eur Respir J* 2019;53:1802130.
- Bloom CI, Franklin C, Bush A, et al. Burden of preschool wheeze and progression to asthma in the UK: population-based cohort 2007 to 2017. *J Allergy Clin Immunol* 2021;147:1949–58.
- Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172:1253–8.
- Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009;123:e519–25.
- Fitzpatrick AM, Jackson DJ, Mauger DT, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138:1608–18.
- Douros K, Everard ML. Time to say goodbye to bronchiolitis, viral wheeze, reactive airways disease. *Front Pediatr* 2020;8:218.
- Brand PLP, Caudri D, Eber E, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J* 2014;43:1172–7.
- Sheikh A, Steiner MFC, Cezard G, et al. Ethnic variations in asthma hospital admission, readmission and death: a retrospective, national cohort study of 4.62 million people in Scotland. *BMC Med* 2016;14:3.

13. Hull SA, McKibben S, Homer K, et al. Asthma prescribing, ethnicity and risk of hospital admission: an analysis of 35,864 linked primary and secondary care records in East London. *NPJ Prim Care Respir Med* 2016;26:16049.
14. Lo D, Beardsmore C, Roland D, et al. Risk factors for asthma attacks and poor control in children: a prospective observational study in UK primary care. *Arch Dis Child* 2022;107:26–31.
15. Kenyon CC, Maltenfort MG, Hubbard RA, et al. Variability in diagnosed asthma in young children in a large pediatric primary care network. *Acad Pediatr* 2020;20:958–66.
16. Petherick ES, Pearce N, Sunyer J, et al. Ethnic and socio-economic differences in the prevalence of wheeze, severe Wheeze, asthma, eczema and medication usage at 4 years of age: findings from the born in bradford birth cohort. *Respir Med* 2016;119:122–9.
17. Panico L, Bartley M, Marmot M, et al. Ethnic variation in childhood asthma and wheezing illnesses: findings from the millennium cohort study. *Int J Epidemiol* 2007;36:1093–102.
18. BTS. British Thoracic society and Scottish intercollegiate network guideline on the management of asthma. 2019.
19. NHSE. Core20PLUS5 – an approach to reducing health inequalities for children and young people. In: NHS England, Eds. 2022.
20. Clinical Practice Research Datalink. CPRD Aurum may 2022 (version 2022.05.001). 2022.
21. Wolf A, Dedman D, Campbell J, et al. Data resource profile: clinical practice research Datalink (CPRD). *Int J Epidemiol* 2019;48:1740–1740g.
22. Clinical Practice Research Datalink. CPRD Aurum small area data (patient) January 2022 (version 2022.01.001). 2022.
23. Mahadevan P, Harley M, Fordyce S, et al. Completeness and representativeness of small area socioeconomic data linked with the UK clinical practice research datalink (CPRD). *J Epidemiol Community Health* 2022;76:880–6.
24. Clinical Practice Research Datalink. CPRD Aurum HES APC January 2022 [data set]. 2022.
25. Clinical Practice Research Datalink. CPRD Aurum HES OP August 2021 (version 2021.08.001) [data set]. 2021.
26. Clinical Practice Research Datalink. CPRD aurum HES A&E August 2021 (version 2021.08.001) [Data set]. 2021.
27. Department for Environment Food & Rural Affairs. Rural urban classification. 2021. Available: <https://www.gov.uk/government/collections/rural-urban-classification>
28. Alsallakh MA, Rodgers SE, Lyons RA, et al. Association of socioeconomic deprivation with asthma care, outcomes, and deaths in Wales: a 5-year national linked primary and secondary care cohort study. *PLoS Med* 2021;18:e1003497.
29. Busby J, Price D, Al-Lehebi R, et al. Impact of socioeconomic status on adult patients with asthma: a population-based cohort study from UK primary care. *J Asthma Allergy* 2021;14:1375–88.
30. Redmond C, Akinoso-Imran AQ, Heaney LG, et al. Socioeconomic disparities in asthma health care utilization, exacerbations, and mortality: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2022;149:1617–27.
31. Asthma + Lung UK. Youngsters experiencing deprivation more likely to have asthma attacks when they return to school. 2023. Available: <https://www.asthmaandlung.org.uk/media/press-releases/youngsters-experiencing-deprivation-more-likely-haveasthma-attacks-when-they>
32. Lucas JA, Marino M, Fankhauser K, et al. Role of social deprivation on asthma care quality among a cohort of children in US community health centres. *BMJ Open* 2021;11:e045131.
33. Netuveli G, Hurwitz B, Levy M, et al. Ethnic variations in UK asthma frequency, morbidity, and health-service use: a systematic review and meta-analysis. *Lancet* 2005;365:312–7.
34. Davidson E, Liu JJ, Sheikh A. The impact of ethnicity on asthma care. *Prim Care Respir J* 2010;19:202–8.
35. Paton J. BTS national paediatric asthma audit summary report National audit period: 1 November – 30 November 2015. 2016.
36. BTS/SIGN. SIGN 158 British guideline on the management of asthma. In: Society SIGNBT, eds. Edinburgh, 2019.
37. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2023.
38. NHS England. Core20Plus5 – an approach to reducing health inequalities for children and young people. 2022. Available: <https://www.england.nhs.uk/about/equality/equality-hub/national-health-care-inequalities-improvement-programme/core20plus5/core20plus5-cyp/>
39. Asthma and Allergy Foundation of America. Asthma disparities in America: a roadmap to reducing burden on racial and ethnic minorities. 2020. Available: <https://aafa.org/asthma-allergy-research/our-research/asthma-disparities-burden-on-minorities/>
40. NIHR. Development of an integrated pathway for preschool asthma/wheeze management (Ip2Am): a mixed methods study. National Institute for Health and Care Research; 2022. Available: <https://fundingawards.nihr.ac.uk/award/NIHR302205>

ARTIGO ORIGINAL

Tendências da pneumonia pneumocócica em adultos hospitalizados com pneumonia adquirida na comunidade ao longo de 10 anos (2013–2023) e o papel do serotipo 3

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RESUMO

Contexto: Com vacinas pneumocócicas de maior valência no horizonte e novas estratégias de imunização para adultos em discussão, o objetivo foi avaliar a contribuição de serotipos pneumocócicos individuais para a carga de pneumonia pneumocócica adquirida na comunidade (CAP). Foram analisadas tendências na epidemiologia da pneumonia pneumocócica em adultos hospitalizados com CAP ao longo de 10 anos, bem como fatores de risco e gravidade associados ao serotipo 3.

Métodos: Foi realizado um estudo de coorte prospectivo com adultos hospitalizados com CAP entre setembro de 2013 e maio de 2023. Os serotipos pneumocócicos foram identificados através de um teste de antígeno urinário 24-valente específico para serotipos. Foram comparadas as tendências na proporção de CAP causada por pneumococos e os serotipos causadores no período pré e pós-pandemia. Fatores de risco e gravidade da pneumonia por serotipo 3 foram comparados a outros serotipos por meio de regressão logística.

Resultados: De 5186 pacientes com CAP, 2193 (42,2%) apresentavam pneumonia pneumocócica. A proporção de CAP devido a pneumococos aumentou em todas as idades entre 2013 e 2023 (36,4%–66,9%, $p < 0,001$). A proporção associada ao serotipo 3 aumentou significativamente de 13,4% (2013) para 48,8% (2023). A pneumonia por serotipo 3 foi associada à idade avançada ($p < 0,001$), sexo masculino (OR ajustado (aOR) 2,22, IC 95% 1,64 a 3,01) e doença renal crônica (aOR 1,81, IC 95% 1,09 a 3,02). Não foi observada associação do serotipo 3 com gravidade, necessidade de cuidados intensivos, mortalidade ou readmissão.

Interpretação: O serotipo 3 é o serotipo predominante na CAP pneumocócica em adultos e tem aumentado, apesar de um programa de imunização infantil maduro, consistente com a ausência de proteção coletiva para este serotipo.

INTRODUCTION

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide,¹ with *Streptococcus pneumoniae* being the most commonly implicated bacterial pathogen.^{2,3}

Pneumococcal vaccines targeting the polysaccharide capsule have made pneumococcal disease at least partially vaccine-preventable, depending on which pneumococcal serotypes are included in the different vaccines, and how effective they are against specific serotypes. In the UK, a seven-valent pneumococcal conjugate vaccine (PCV7) was introduced to the childhood immunisation schedule in 2006 and replaced in 2010 by 13-valent vaccine (PCV13). For adults aged ≥ 65 years and those aged ≥ 2 years in a clinical risk group for pneumococcal disease, a single dose of pneumo-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Following the introduction of pneumococcal conjugate vaccines (PCVs) to the infant immunisation programme in 2006, vaccine-serotype invasive pneumococcal disease (IPD) declined across all ages due to direct and indirect protection but more recently the incidence of IPD in children due to serotype 3 has been increasing. It has been reported that compared with other serotypes, serotype 3 may be linked to increased mortality in the elderly, and to respiratory failure and septic shock.

WHAT THIS STUDY ADDS

► Over a 10-year period, including years before, during and after the COVID-19 pandemic, the proportion of adult community-acquired pneumonia (CAP) due to pneumococcus increased, driven predominantly by serotype 3. This is consistent with a lack of adequate herd protection against adult serotype 3 disease from the infant pneumococcal vaccination programme.
► Serotype 3 pneumococcal CAP was associated with increased age, male sex and chronic renal disease, but not with increased severity or poorer outcomes compared with other serotypes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► A 21-valent PCV is imminent and other higher-valency PCVs are currently under development. The results from this study add to the evidence on changing pneumococcal epidemiology and will contribute to vaccine policy-making decisions, including indirect versus direct adult immunisation strategies and cost-effectiveness analyses.

coccal polysaccharide vaccine (PPV23) has been recommended since 2003,⁴ although its effectiveness in preventing non-invasive pneumonia is likely to be modest.⁵

PCV implementation has been associated with large declines in vaccine-serotype invasive pneumococcal disease (IPD) across all age groups due to direct and indirect protection but with an increase in disease caused by non-PCV serotypes (serotype replacement).^{6,7} However, several studies from different countries have indicated that direct and indirect protection against serotype 3 is lower than for other serotypes,^{8–10} and the incidence of serotype 3 IPD in children has been increasing despite the use of PCV13 in the infant immunisation programme.¹¹ Moreover, there have been reports that compared with other serotypes, serotype 3 may be linked to higher mortality in the elderly,¹² septic shock¹³ and respiratory failure.¹⁴

With more than 100 pneumococcal serotypes, new pneumococcal vaccines targeting an increasing number of serotypes are on the horizon, including PCV21,¹⁵ PCV24 and PCV30+.¹⁶ PCV immunisation is currently only available for children and the initial herd protection effects on adult CAP are now more limited due to changes to the prevailing serotypes. New adult immunisation strategies have been suggested as a means to overcome current limitations in the control of adult pneumococcal disease. An understanding of the contribution of individual pneumococcal serotypes to the burden of pneumococcal CAP is, therefore, important for the development of an updated pneumococcal vaccination policy.

In this study, we employed a 24-valent serotype-specific urinary antigen detection (ssUAD) assay to (a) determine trends in hospitalised pneumococcal pneumonia and the epidemiology of

pneumococcal serotypes over a 10-year period, which included the pre-COVID-19 and post-COVID-19 pandemic period and (b) examine the role of serotype 3 over this period, including risk factors and severity of serotype 3 CAP compared with other serotypes in a cohort of adults with predominantly non-invasive pneumonia. By including data from 2020 to the end of this long-running cohort study, we build on our previously published findings^{17,18} and aim to summarise the changing epidemiology of pneumococcal CAP that has occurred during the last 10 years, including data from the COVID-19 pandemic period which we have not previously reported.

METHODS

Study design

The methods for this prospective cohort study have been previously described¹⁸ (see online supplement) For this analysis, data were collected for adults ≥ 16 years old hospitalised with CAP in two teaching hospitals in Nottingham between September 2013 and May 2023. Recruitment was paused for a period during the pandemic (13 March 2020–2 August 2020). From August 2020 onwards, patients testing positive for SARS-CoV2 were included if they had radiographic evidence of pneumonia.

Microbiology

Urine samples were obtained within 48 hours of admission for pneumococcal-specific UAD using the Binax-NOW (Alere, Stock-

Table 1 Baseline characteristics, disease severity and outcomes in community-acquired pneumonia (CAP) and pneumococcal pneumonia

Patient characteristics	Whole cohort (n=5186)	Pneumococcal cohort (n=2193)	Non-pneumococcal CAP (n=2993)	P value
Demographics				
Age, median; years (IQR)	71.1 (56.5–80.9)	70.4 (56.9–80.4)	71.6 (56.2–81.3)	0.26
Male (%)	2762 (53.4)	1190/2188 (54.4)	1572/2980 (52.8)	0.24
Comorbid disease				
Smoking status*				
Never smoked	1557 (30.9)	623 (29.0)	934 (32.3)	
Ex-smoker	2353 (46.8)	977 (45.5)	1376 (47.6)	<0.001
Current smoker	1124 (22.4)	545 (25.4)	579 (20.0)	
COPD	1264 (24.4)	579 (26.4)	685 (22.9)	0.004
Diabetes mellitus	870 (16.8)	361 (16.5)	509 (17.0)	0.60
Cerebrovascular disease	408 (7.9)	173 (7.9)	235 (7.9)	0.96
Congestive cardiac failure	351 (6.8)	144 (6.6)	207 (6.9)	0.62
Ischaemic heart disease	632 (12.2)	249 (11.4)	383 (12.8)	0.12
Asthma	601 (11.6)	260 (11.8)	341 (11.4)	0.61
Cognitive impairment	177 (3.4)	65 (3.0)	112 (3.7)	0.13
Liver disease	92 (1.8)	38 (1.7)	54 (1.8)	0.85
Kidney disease	533 (10.3)	234 (10.7)	299 (10.0)	0.43
Immunocompromised	231 (4.4)	223 (5.1)	119 (4.0)	0.05
PPV23 receipt*	1853 (37.3)	812 (38.4)	1041 (36.5)	0.19
Severity				
CURB65 0–1 (low)	2531/5160 (49.0)	1026/2183 (47.0)	1505/2977 (50.6)	
CURB65 2 (moderate)	1522 (29.5)	642 (29.4)	880 (29.6)	0.003
CURB65 3–5 (high)	1107 (21.4)	515 (23.6)	592 (19.9)	
Outcome				
30-day mortality	433 (8.3)	147 (6.7)	286 (9.6)	<0.001
30-day readmission	592/4753 (12.4)	235/2046 (11.5)	357/2707 (13.2)	0.08
ICU/HDU admission	410 (7.9)	205 (9.3)	205 (6.8)	0.001

Data are presented as n (%) or median (IQR).

CURB-65: confusion, urea > 7 mmol/L, respiratory rate > 30 /min, blood pressure < 90 mm Hg systolic, < 60 mm Hg (diastolic), age ≥ 65 years.

p-values < 0.05 are indicated in bold.

*Data regarding smoking status available for 2145 and 2889 patients, and for PPV23 receipt in 2117 and 2849 patients in the pneumococcal and non-pneumococcal cohort, respectively.

COPD, chronic obstructive pulmonary disease; ICU/HDU, intensive care unit/high dependency unit; PPV23, pneumococcal polysaccharide vaccine.

Table 2 Trend in proportion of all-cause CAP attributable to pneumococcus between 2013 and 2023

Study year	Pneumococcal CAP (N)	All-Cause CAP (N)	% CAP due to pneumococcus
1 September 2013–31 August 2014	180	495	36.4
1 September 2014–31 August 2015	202	583	34.7
1 September 2015–31 August 2016	165	516	32.0
1 September 2016–31 August 2017	248	644	38.5
1 September 2017–31 August 2018	283	697	40.6
1 September 2018–31 August 2019	321	734	43.7
1 September 2019–31 August 2020*†	238	570	41.8
1 September 2020–31 August 2021*	125	285	43.8
1 September 2021–31 August 2022	219	345	63.5
1 September 2022–31 May 2023	212	317	66.9
Total	2193	5186	42.3
P value for trend for entire study period, excluding patients admitted between 13 March 2020 and 31 August 2021 <0.001.			
P value for trend from 2013 to 13 March 2020 only=<0.001.			
*Lockdown measures for SARS-CoV2 pandemic in force.			
†The study was paused for recruitment between 13 March 2020 and 2 August 2020 due to the COVID-19 pandemic.			
CAP, community-acquired pneumonia.			

port, UK) assay for pneumococcal C-polysaccharide urinary antigen and for pneumococcal serotype-specific urinary antigen testing using a validated multiplex immunoassay (Bioplex-24)¹⁹ (detailed in online supplement). ‘Non-ssUAD’ pneumococci were defined as those for which cell-wall polysaccharide was detected but the Bioplex-24 assay was not able to generate a serotype-specific result. Vaccine types were classified according to the serotypes included in their formulation (online supplement). Blood cultures were taken at the discretion of the treating clinician.

Patients were considered to have pneumococcal CAP if they met ≥ 1 criteria: (a) positive pneumococcal UAD or (b) blood culture positive for *S. pneumoniae* or (c) detection of a pneumococcal serotype or cell wall polysaccharide by the Bioplex24 assay.

Statistical analysis

Categorical variables for baseline demographics, disease severity and clinical outcomes (critical care admission, 30-day mortality and readmission within 30 days) were expressed as frequencies and as percentages and compared using Pearson's χ^2 or Fisher's exact tests. Continuous variables were summarised as medians with IQR and compared using the Mann-Whitney U test. To account for interyear variability, a restricted cubic spline model with five knots based on Harrell's recommended percentiles²⁰ was used to describe trends in patient characteristics, risk factors and outcomes over time. We defined ‘prepandemic’ as September 2013–12 March 2020, the ‘pandemic period’ as 13 March 2020–31 August 2021 and ‘postrestriction period’ as 1 September 2021–31 May 2022. Patients admitted during the ‘pandemic period’ were excluded from the tests for trend of patient characteristics and severity as patients admitted at the height of the pandemic may have been sicker, and therefore, selectively tested and included.

We used univariable and multivariable logistic regression models to compare associations between pneumonia and the characteristics and outcomes of (1) patients with pneumococcal pneumo-

nia versus non-pneumococcal pneumococcal pneumonia and (2) patients with single-serotype 3 disease versus patients with a different single serotype identified. We presented the results as ORs with 95% CIs and the corresponding p value. As there were no a priori restrictions on participants being enrolled more than once over the course of the study and it was not possible to link individuals to their separate admissions, the unit of analysis was each admission rather than individual participant. Variables for inclusion in the multivariable analysis were purposefully selected based on clinical risk factors outlined in the UK Health Security Agency's ‘Immunisation against Infectious Disease’ (The Green Book)⁴ and previous studies²¹ and were included in the final model if the p value was <0.2 on univariate analysis of demographic characteristics. Outcome analyses were adjusted for variables which altered the crude OR by $>10\%$. To minimise bias in those who were excluded from whole case analysis due to incomplete records, we used multiple imputation with five imputations including all analysis variables under the assumption that data are missing at random (see online supplement for details of missing observations and the multiple imputation model).

Statistical analyses were conducted by using Stata/SE V.18.0 (StataCorp. 2023. Stata Statistical Software: Release V.18., Stata-Corp).

RESULTS

Baseline characteristics

7078 patients with radiographically confirmed all-cause pneumonia were admitted between September 2013 and May 2023, with 5186 (73.3%) giving their consent to take part in the study. Urine for pneumococcal testing was available for 5020 (96.8%) consented patients, of which 4933 (98.3%) were tested using Bioplex-24, and 87 (1.7%) were tested only using BinaxNOW.

Based on blood culture and Bioplex-24/BinaxNOW UAD results, pneumococcal pneumonia was diagnosed in 2193 included patients (42.3%). Diagnosis was based solely on the detection of a serotype in urine by Bioplex-24 in 1191 patients (54.3%), and by BinaxNow only in 139 (6.3%). Both Bioplex-24 and BinaxNOW were positive in 794 patients (36.2%). A serotype was detected in blood but not by Bioplex-24 in 24 patients (22 Bioplex not performed, 2 Bioplex negative) (online supplemental figure 1). Serotype 8 accounted for 36.8% of blood culture serotypes, followed by serotypes 3 (9.6%), 19A (8.1%) and 12F (6.7%) (online supplemental figure 2).

The median age of the study cohort was 71.1 years (IQR 56.5–80.9), 2762 (53.4%) were male and pneumonia severity was low, moderate and high in 2531 (49.0%), 1522 (29.5%) and 1107 (21.4%), respectively, based on the CURB-65 score. Critical care admission was required in 410 (7.9%) patients, and 433 (8.3%) patients died within 30 days of admission (table 1).

On multivariable analysis, current smoking, COPD and immunocompromise were independently associated with the risk of pneumococcal pneumonia (adjusted OR, aOR 1.36, 95% CI 1.16 to 1.60; aOR 1.18, 95% CI 1.02 to 1.36; and aOR 1.32, 95% CI 1.01 to 1.72 respectively) (online supplemental table 1). Compared with non-pneumococcal CAP, patients with pneumococcal CAP were more likely to be admitted to critical care (aOR 1.36, 95% CI 1.10 to 1.66) and have higher CURB-65 scores (aOR 1.16, 95% CI 1.08 to 1.26), although the odds of death within 30 days were lower (aOR 0.64, 95% CI 0.52 to 0.79) (table 1 and online supplemental table 2).

Trends between 2013 and 2023: prepandemic versus postpandemic

Proportion of CAP due to *Streptococcus pneumoniae*

The proportion of CAP attributable to pneumococcus increased significantly over the 10 years for all ages, from 36.4% in 2013–2014 to 66.9% in 2022–2023 ($p<0.001$). This upward trend was observed prepandemic (p value for trend <0.001) (table 2) but was particularly marked in all age groups from 2020 when COVID-19 pandemic restrictions were introduced in the UK (figure 1). In



Figure 1 The absolute proportion of community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae* between 2013 and 2023 by study year and according to age group. The numerator is the number of patients with pneumococcal pneumonia per age group and the denominator is the total number of patients admitted with all-cause CAP for that age group.

the final winter season (2022–2023), the proportion of CAP attributed to pneumococcus remained higher than prepandemic, particularly in patients ≥ 75 years although the upward trend was less marked or reversing in younger age groups (figure 1). The proportion of patients with pneumococcal pneumonia who were bacteraemic fell after the onset of the pandemic and was lowest during 2021–2022 (4.6%) but had increased to 11.3% in 2022–2023 and was similar to prepandemic proportions (figure 2).

Trends in demographics and severity

Patient characteristics for the prepandemic period and over the entire study period are described in table 3 and online supplemental table 3. The proportion of patients who had ever received PPV23 vaccine increased from 36.2% in 2013 to 50.5% in 2023, but after adjusting for age, sex and chronic obstructive pulmonary disease (COPD) and excluding patients admitted between March 2020 and August 2021, there was an overall decreased trend in the proportion of patients of vaccinated over the study period (p value for trend=0.02).

The proportion of patients with pneumococcal CAP dying within 30 days varied from year to year, although the overall trend was towards increasing mortality ($p=0.02$). Mortality was highest between September 2020 and August 2021 (table 3). From the start of the pandemic to the end of the study, 90/923 (9.8%) of patients with all-cause CAP tested positive for SARS-CoV2 on admission. Mortality was significantly higher in those who were SARS-CoV2 positive (15/90, 16.7%) compared with those who were negative (69/833, 7.2%) ($p=0.009$) but did not differ significantly between SARS-CoV2 positive pneumococcal CAP (7/50, 14.0%) and SARS-CoV2 positive non-pneumococcal CAP (8/40, 20.0%) ($p=0.45$).

Readmission rates and critical care admissions did not change significantly over the study period.

Serotype distribution

The most prevalent serotypes over the study period were serotypes 3 (29.3%), 8 (21.4%), non-ssUAD (7.8%), 15A (4.9%) and 9N (4.1%). Trends in the distribution of individual serotypes over the study period are shown in figure 3 and online supplemental table 4. Over the 10 years, there was a marked steady increase in serotype 3, accounting for 13.4% of pneumococcal CAP in 2013 to 48.8% in 2023. Serotype 8, the second most prevalent serotype, accounted for between 17.0% and 19.7% of pneumococcal CAP prepandemic but peaked at 37.4% between September 2020 and August 2021. By mid-2023, the proportion of CAP in which serotype 8 was implicated had decreased back to 19.9%, similar to that seen prepandemic. Over the study, there was a decrease in proportion of CAP caused by non-ssUAD pneumococci from 12.4% in 2013–2014 to 2.6% in 2022–2023. Other serotypes in which there was a decline in proportions were serotypes 7F (PCV13), 12F (PCV20), 15A and 16F (PCV21) (online supplemental table 4).

Between 2013 and 2023, there was an increase in the proportion of multiple serotypes detected in the Bioplex-24 assay, from 9.1% to 36.6% (p value for trend <0.001). In 2021–2022, 52.4% of detections were multiple serotypes. Serotype 3 was the most prevalent serotype detected with one or more other serotype in 313 of 466 (67.2%) patients with multiple serotype detections. The combination of serotypes 3 plus 8 accounted for 183 (39.3%) of multiple detections followed by serotype 5 plus serogroup 15 (5.4%) (online supplemental figure 3).

Figure 4 shows the trend by pneumococcal vaccine type over the study period. The proportion of pneumococcal CAP caused by PCV13 serotypes increased significantly between 2013 and 2023 (p value for trend=0.0005), ranging from 22.6% in 2014–2015 to 64.4% in 2022–2023. The increasing trend was occurring prepandemic (p value for trend=0.01). When serotype 3 was excluded,

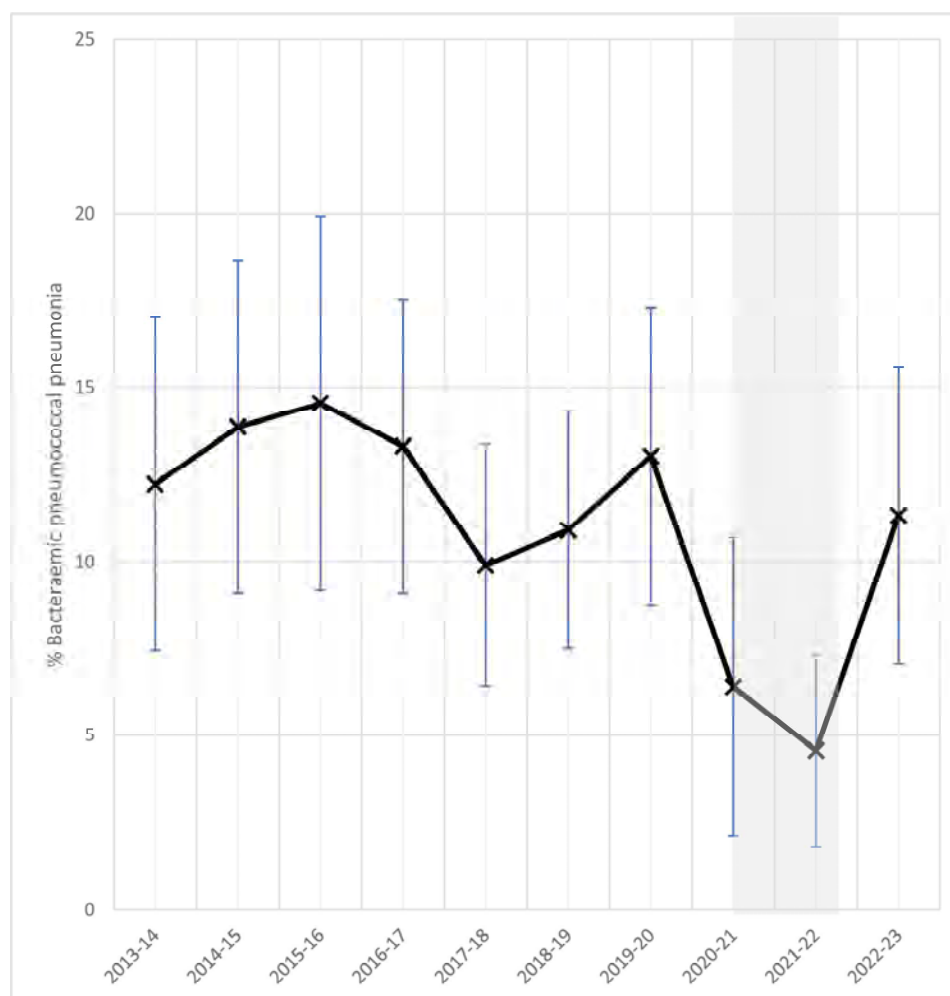


Figure 2 The absolute proportion of hospitalised patients with pneumonia due to *Streptococcus pneumoniae* who were bacteraemic during each year of the study from 2013 to 2023.

Table 3 Trends in characteristics of pneumococcal CAP patients between 2013 and 2023 by study year

	Study year (number of patients)										P value for trend
	2013–2014 (n=180)	2014–2015 (n=202)	2015–2016 (n=165)	2016–2017 (n=248)	2017–2018 (n=283)	2018–2019 (n=321)	2019–2020 (n=238)	2020–2021 (n=125)	2021–2022 (n=219)	2022–2023 (n=212)	
Median age (IQR)	67.4 (49.9–80.1)	68.0 (51.5–77.4)	66.9 (50.9–78.7)	70.1 (53.9–81.1)	71.8 (59.2–81.7)	71.9 (58.4–81.5)	72.8 (60.2–81.3)	71.6 (58.5–80.3)	69.5 (60.0–78.6)	70.8 (60.1–80.0)	0.14*†
Sex, male (%)	91 (50.6)	96 (47.5)	86 (52.1)	110 (44.4)	132 (46.6)	169 (52.2)	136 (56.7)	99 (79.2)	136 (62.1)	135 (63.7)	0.22*‡
PPV23 receipt (%)	59/163 (36.2)	80/189 (52.3)	46/153 (29.9)	79/234 (33.8)	96/262 (36.6)	100/321 (31.2)	81/238 (34.0)	55/125 (44.0)	109/219 (49.8)	107/212 (50.5)	0.02*‡
Severity											
30-day mortality (%)	8 (4.4)	11 (5.4)	4 (2.4)	19 (7.7)	12 (4.2)	30 (9.3)	20 (8.4)	14 (11.2)	20 (9.1)	9 (9.1)	0.02*§
Readmitted (%)	20/172 (11.6)	19/191 (9.9)	12/161 (7.4)	20/223 (9.0)	25/271 (9.2)	46/291 (15.8)	34/218 (15.6)	12/111 (10.8)	30/199 (19.6)	20/203 (9.8)	0.63*¶
Critical care admission (%)	18 (10.0)	22 (10.9)	19 (11.5)	28 (11.3)	22 (7.8)	29 (9.0)	27 (11.3)	12 (9.6)	15 (6.8)	13 (6.1)	0.52***

Trends in characteristics and outcomes in patients hospitalised with pneumococcal CAP between 2013 and 2023 by study year. Absolute numbers and the corresponding percentages are presented for each variable for each year. Estimated p values for trends were obtained by restricted cubic spline regression with five knots at admission dates of 6 April 2014, 24 June 2016, 5 February 2018, 2 September 2019 and 25 December 2022 for the entire study period, and at 12 March 2014, 5 January 2016, 9 August 2017, 12 November 2018 and 29 December 2019 for the prepandemic period only, based on Harrell's recommended percentiles.

p-values <0.05 are indicated in bold.

*P value for trend across the 10-year study period excludes patients admitted between 13 March 2020 and 31 August 2021.

†P value for prepandemic trend between 2013–2014 and 2019–2020 only.

‡Adjusted for sex, PPV23 receipt and COPD.

§Adjusted for age, smoking status and CURB65.

¶Adjusted for age, PPV23 receipt and COPD.

***Adjusted for age, PPV23 receipt and CURB65.

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; PPV23, pneumococcal polysaccharide vaccine.

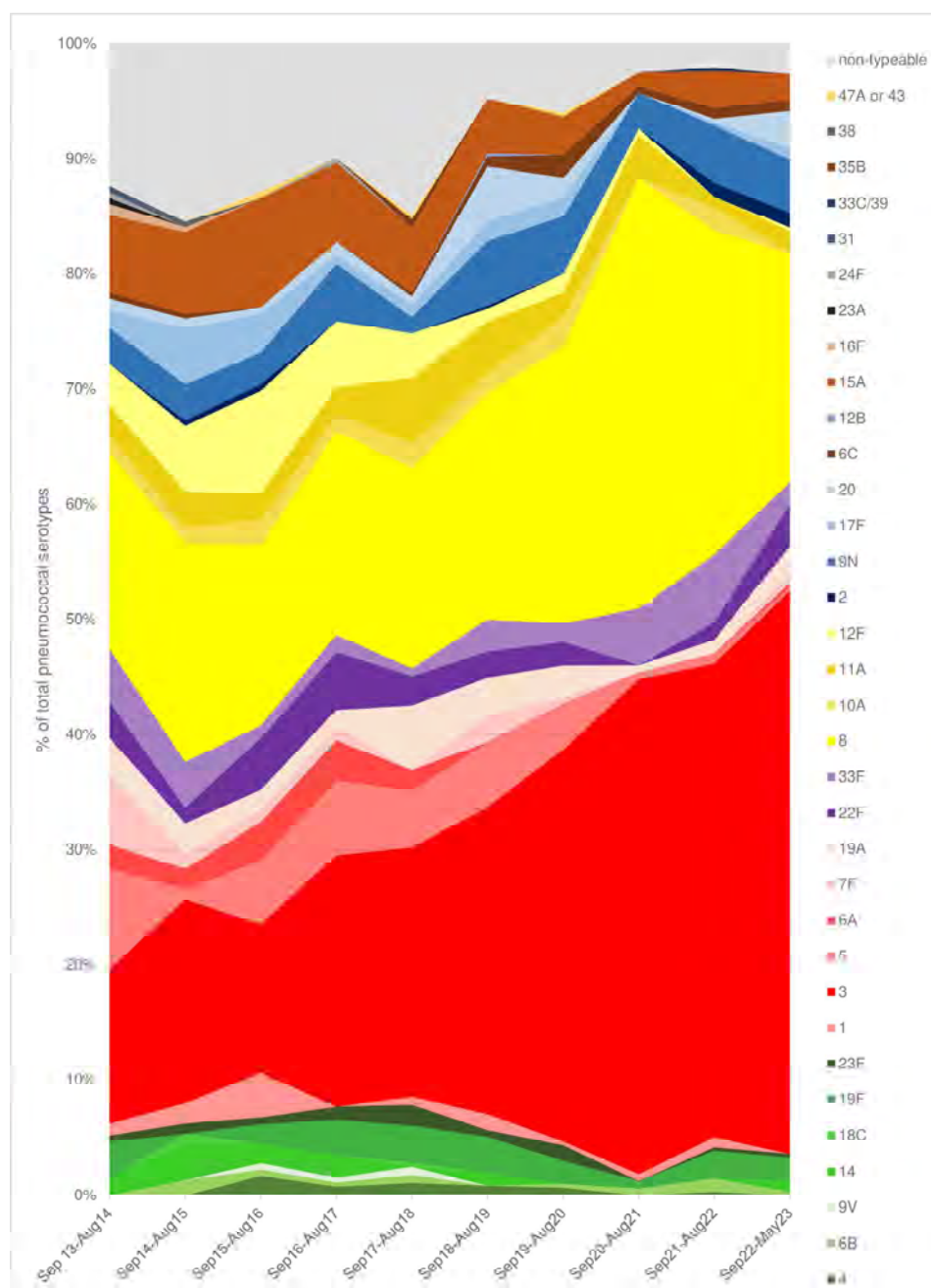


Figure 3 Stacked area plot showing the relative proportion of individual pneumococcal serotypes detected by urinary Bioplex-24 assay for each year of the study between 2013 and 2023. The numerator is the number of detections of each individual serotype and the denominator is the total number of serotype detections for each year.

the trend for the remaining PCV13 serotypes was statistically non-significant ($p=0.29$). The proportion of PCV20-nonPCV13 serotypes peaked at 37.9% in 2020–2021 but decreased in 2021–2022 (13.0%) and again in 2022–2023 (11.4%), corresponding to the pattern observed with serotype 8. Non-vaccine serotypes decreased over the study ($p=0.006$) from a peak of 28.7% in 2014–2015 to 6.9% in 2020–2021. Over the study period, 44.2% of serotypes were covered by PCV13, 49.6% by PCV15 and 78.3% by PCV20. The PCV21 would have covered 80.8% of all serotypes (online supplemental table 5).

Serotype 3 pneumonia

Older patients were more likely to have CAP due to serotype three compared with people aged 16–49 years (p value for trend by increasing age category <0.001 , aOR for 75–84 years 2.25, 95% CI 1.50 to 3.41 and ≥ 85 years aOR 2.52, 95% CI 1.40 to 4.52). Male sex, chronic renal disease and asthma were also associated with the risk of serotype 3 CAP compared with other serotypes (aOR 2.22, 95% CI 1.64 to 3.01; aOR 1.81, 95% CI

1.09 to 3.02 and aOR 1.60, 95% CI 1.08 to 2.38, respectively) (table 4).

Patients with serotype 3 CAP were less likely to have bacteraemia compared with patients with other serotypes (aOR 0.43, 95% CI 0.27 to 0.68). After adjusting for age, we did not observe any significant differences in severity (as measured by CURB-65), critical care admission, 30-day mortality or 30-day readmission (table 5).

DISCUSSION

Over the course of 10 years up to mid-2023, the proportion of hospitalised all-cause pneumonia caused by *S. pneumoniae* has been increasing. Although the absolute number of all-cause pneumonia cases declined during 2020–2021, coinciding with the COVID-19 pandemic, the upward trend in the proportion due to pneumococcus continued to increase and rose markedly in all age groups in 2021–2022. In the UK, COVID-19 restrictions were lifted in July 2021. The societal and behavioural changes during the pandemic resulted in less exposure to patho-

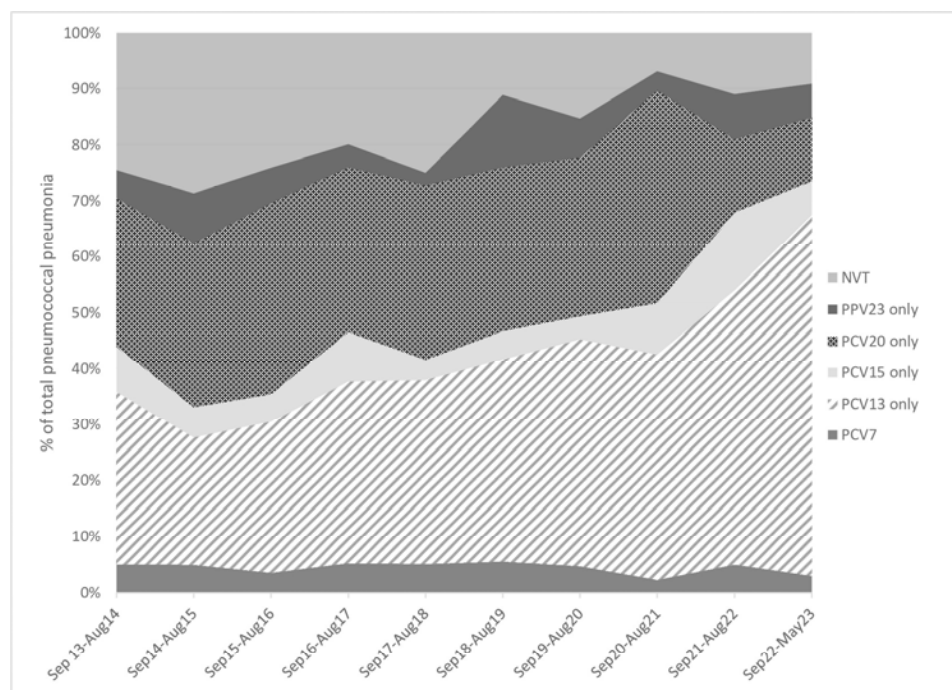


Figure 4 Stacked area plot showing the relative proportion of pneumococcal serotypes detected during each year of the study which are covered by pneumococcal vaccines: PCV7, PCV13-nonPCV7, PCV15-nonPCV13, PCV20-only, PPV23-only serotypes and non-vaccine types (serotypes not covered by these vaccines or non-BioPlex24 serotypes). PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F Additional PCV13 serotypes: 1, 3, 5, 6A, 7F, 19A, PCV15nonPCV13 serotypes: 22F, 33F PCV20non13/15 serotypes: 8, 10A, 11A, 12F, 15B PPV23non20 serotypes: 2, 9N, 17F, 20. NVT, non-vaccine types; PCV7, seven-valent pneumococcal conjugate vaccine.

gens spread by the respiratory route and led to observed alterations to patterns of community circulation of respiratory viral pathogens in many countries.²² This likely affected the contribution to all-cause pneumonia from other respiratory pathogens and may explain the higher relative contribution from pneumococcus during this period. Thresholds for hospital admission changed during this period and patients with milder illness due to non-pneumococcal pneumonia may have been less likely to be hospitalised, so to a certain extent the marked increase in proportion of CAP due to pneumococcus observed after 2020 may reflect a change in the hospitalised population. In the final year, the proportion of CAP attributable to pneumococcus was declining, or at least stabilising in younger age groups, but remained very high in people aged 75 years and above. Ongoing observation is required to assess whether the proportion of pneumococcal pneumonia in older people will return to pre-pandemic levels; potentially influenced by SARS-CoV2 as an endemic pathogen, changes in pneumococcal vaccine coverage and new or altered immunisation programmes against respiratory pathogens.

Most cases of pneumococcal pneumonia are not invasive and prior to the pandemic between 10% and 15% of our patients had pneumococcal bacteraemia. This declined sharply when COVID-19 restrictions were in place and remained low in 2021–2022 after restrictions had been eased. This observation is in accordance with a national surveillance study of invasive pneumococcal disease (IPD) in England,²³ although we noted that, in 2022–2023, the proportions of invasive disease had returned to >10%, similar to proportions expected before the pandemic. Co-colonisation with other respiratory pathogens has been linked to high pneumococcal nasopharyngeal carriage density,²⁴ which in turn has been identified as a risk factor for IPD.²⁵ The decreased circulation of other respiratory pathogens between 2020 and 2022 may, therefore, help to explain our observation. Despite the observation that the pandemic was associated with reductions in IPD, we observed an increase proportionately in pneumococcal pneumonia. Post-2020, remote primary care consultations increased and this has been associated with a 23% increase in antibiotic prescribing in adults with acute respiratory infections.^{26,27} Pre-admission antibiotics would have a much greater influence on blood culture posi-

tivity than on Bioplex positivity, and this may partly explain the difference in IPD and non-culture-based detection of pneumococcal infection.

The upward trend in pneumococcal pneumonia appears to have been driven largely by serotype 3, which at the end of our study accounted for almost half of pneumococcal cases. The predominance of serotype 3 has also been seen in patients with IPD in England²³ and in non-invasive pneumococcal CAP elsewhere in Europe.^{28–30} In comparison to our findings, a recent study in Bristol 2021–2022 found a lower overall proportion of pneumococcal pneumonia in patients with CAP, with serotype 8 most prevalent.³¹ A different ssUAD assay was used in the Bristol study which may have different test characteristics for serotype 3 resulting in the discrepancies in findings; for instance, differences in the ability to detect pneumococcal colonisation. Whole genome sequencing has identified that between 2017–2018 and 2022–2023 most IPD cases of serotype 3 belonged to very similar circulating strains, with most belonging to Global Pneumococcal Sequencing Cluster 12.²³ Although we do not have genomic data to confirm this for our pneumonia cases, it is feasible that we are also observing expansion of a previously circulating strain of serotype 3.

In patients with confirmed IPD, serotype 3 has been associated with a higher incidence of septic shock,¹³ empyema and complicated pneumonia,³² and major adverse cardiac events.³³ However, we found no evidence that serotype 3 caused more severe disease, increased mortality or the requirement for critical care compared with other serotypes. A comparable study in patients with CAP in Germany (CAPNETZ) reported that patients with serotype 3 CAP required oxygen administration more frequently than patients with CAP due to other serotypes, but similar to our findings, they did not find evidence that serotype 3 was associated with higher ICU admission rates, clinical cure and/or 28-day mortality compared with other serotypes.²⁸

The burden of serotype 3 disease in older adults remains substantial despite the introduction of PCV13 immunisation in children in the UK in 2010. We found that age and male sex are independent predictors of serotype 3 CAP, consistent with previously reported associations.^{34,35} With the proportion of the UK population aged ≥65 years rising from 16.4% in 2011 to 18.6% in

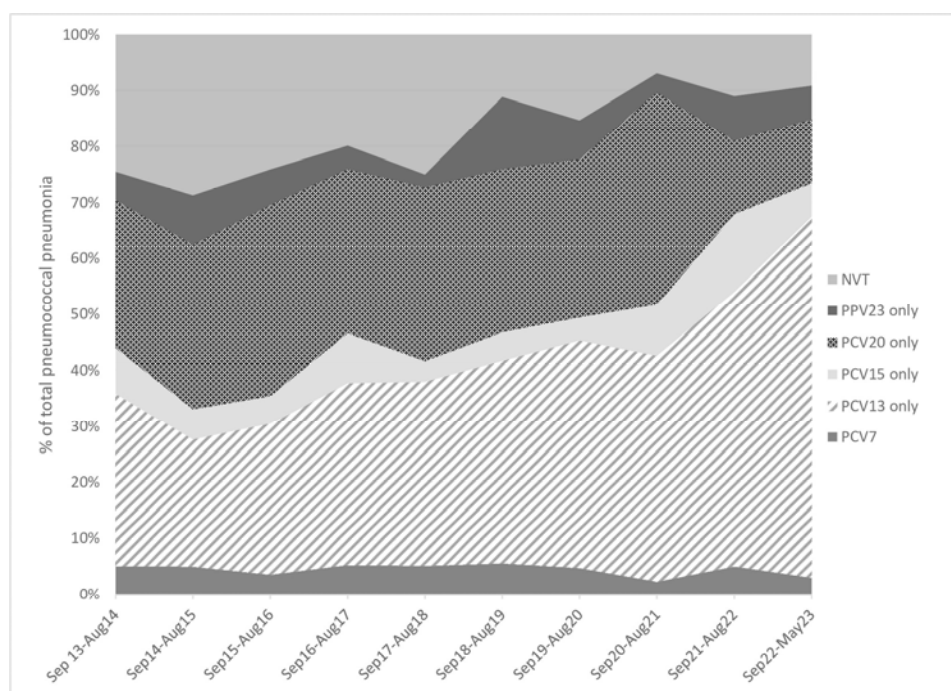


Figure 4 Stacked area plot showing the relative proportion of pneumococcal serotypes detected during each year of the study which are covered by pneumococcal vaccines: PCV7, PCV13-nonPCV7, PCV15-nonPCV13, PCV20-only, PPV23-only serotypes and non-vaccine types (serotypes not covered by these vaccines or non-Bioplex24 serotypes). PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F Additional PCV13 serotypes: 1, 3, 5, 6A, 7F, 19A, PCV15nonPCV13 serotypes: 22F, 33F PCV20non13/15 serotypes: 8, 10A, 11A, 12F, 15B PPV23non20 serotypes: 2, 9N, 17F, 20. NVT, non-vaccine types; PCV7, seven-valent pneumococcal conjugate vaccine.

2021,³⁶ an increasingly older population may account for some of the increased burden of serotype 3 observed. Furthermore, despite an overall decline in childhood carriage of PCV13 serotypes since the introduction of childhood immunisation, carriage of serotype 3 has persisted in the UK. The indirect protective effects of childhood PCV13 immunisation against IPD in adults have been observed to be lower for serotype 3^{8,11,37}; consistent with the observations with respect to serotype 3 pneumonia in adults. These factors taken together likely explain the ongoing relative increase in adult serotype 3 pneumonia despite the current infant PCV13 immunisation programme.³⁸ In 2020, the UK moved from a 2+1 childhood immunisation schedule to 1+1.³⁹ A recent surveillance study of IPD, conducted 3 years after the introduction of the revised schedule, did not observe significantly different rates of breakthrough infections or vaccine failures in children who received the reduced schedule compared with those who received the 2+1 PCV13 schedule.²³ Considering the relatively recent schedule implementation and the likely disruptive effects of the pandemic on the epidemiology of pneumococcal disease, the impact of the 1+1 change on adult pneumococcal pneumonia cannot be adequately assessed in this study.

Implications of this study

Our findings underline the importance of ongoing efforts to prevent and reduce the impacts of pneumococcal pneumonia on adults, particularly older adults. The UK population aged ≥ 85 years is projected to increase by one million over the next 15 years.⁴⁰ Driven largely by the ageing population, the number of people living with chronic kidney disease is also forecast to increase to 7.6 million by 2033.⁴¹ These changes may impel further increases in serotype 3 disease unless other interventions are introduced. In addition to the indirect herd protection from childhood programmes, the further role of direct vaccination of adults needs to be considered. This is especially pertinent now given the increased availability of higher-valent conjugate vaccines, including a PCV21 specifically designed to cover serotypes affecting adults, which may provide better protection than the currently used PPV23.

Our study has several strengths. It is a large prospective cohort study conducted over many years allowing us to accrue data on a

large number of hospitalised patients with all-cause CAP and to compare trends in pneumococcal pneumonia as a whole and in the distribution of pneumococcal serotypes before and after the pandemic. Use of the urinary 24-valent Bioplex-24 assay allowed detection of serotypes implicated in non-invasive pneumococcal pneumonia that would otherwise not be classified by culture-based methods.

There are limitations to this study. The 24-valent ssUAD assay was the main tool for identifying pneumococcal disease so it is likely that we missed some cases of pneumococcal disease in patients who did not have a urine sample tested by the ssUAD assay. Although $>80\%$ of serotypes over the 10 years were PCV21 serotypes, we likely underestimated PCV21-CAP as not all PCV21 serotypes are detected by the current 24-valent assay. There are recognised cross-reactions in the Bioplex-24 assay with serotypes which are not targeted in the assay, where the serotype was designated based on the predominant serotype using national IPD data. This may have caused under-reporting of less common non-vaccine serotypes and thus underestimation of the prevalence of non-vaccine-type pneumonia.

As there were no *a priori* restrictions on multiple recruitment of participants in different study years and we were not able to link individual participants to their separate admissions, prior CAP is a confounder that could plausibly change the effect for many risks and outcomes modelled and is a limitation which needs to be recognised, although fewer than 5% of participants were enrolled more than once over the course of the study. Also, the study was conducted at a single centre and may not be representative of pneumococcal and serotype trends elsewhere in the UK. However, the results from two further UK sites over a 2-year period are similar to our findings.¹⁷ Changes in the admission process for patients with pneumonia in Nottingham occurred during the pandemic, with most patients directed to one hospital, and this may also have altered hospitalisation thresholds. In addition, after the recruitment pause was lifted, it was only possible to recruit patients from that one hospital due to staff redeployment to urgent COVID-19 studies; therefore, we could not be certain that all potentially eligible adults were identified for study inclusion. Given these differences, it was deemed inappropriate to calculate and compare

Table 4 Risk factors for serotype 3 CAP compared with other pneumococcal serotypes

	Serotype 3 CAP N=441 (%)	Non-ST3 CAP N=1133 (%)	OR (95% CI)	P value	aOR (95% CI)	P value
Baseline characteristics						
Median age (IQR)	73.3 (62.7–82.1)	67.5 (53.0–78.5)		<0.001		
Age category						
16–49 years	41 (9.3)	247 (21.8)	Ref		Ref†	
50–64 years	95 (21.5)	255 (22.5)	1.71 (1.19 to 2.47)		1.63 (1.12 to 2.37)	
65–74 years	105 (23.8)	270 (23.8)	2.09 (1.33 to 3.27)	<0.001*	1.78 (1.11 to 2.87)	0.006*
75–84 years	122 (27.6)	229 (20.2)	2.69 (1.86 to 3.89)		2.25 (1.50 to 3.41)	
≥85 years	78 (17.7)	132 (11.6)	3.06 (1.86 to 5.04)		2.52 (1.40 to 4.52)	
Sex, male	297 (67.3)	549 (48.4)	2.17 (1.57 to 3.00)	0.001	2.22 (1.64 to 3.01)†	<0.001
PPV23 vaccine receipt	182/434 (41.9)	357/1081 (33.0)	1.49 (1.21 to 1.84)	0.001	1.22 (1.01 to 1.48)†	0.04
Smoking						
Never	131/436 (30.0)	310/1103 (28.1)	Ref		Ref†	
Ex	209 (47.9)	480 (43.5)	1.10 (0.75 to 1.61)	0.42*	0.92 (0.60 to 1.40)	0.70*
Current	96 (22.0)	313 (28.4)	0.79 (0.47 to 1.33)		0.94 (0.61 to 1.46)	
Liver disease	6 (1.4)	23 (2.0)	0.57 (0.26 to 1.22)	0.14	0.54 (0.25 to 1.17)†	0.11
Chronic kidney disease	71 (16.1)	84 (7.4)	2.20 (1.38 to 3.51)	0.005	1.81 (1.09 to 3.02)†	0.03
Chronic cardiac failure	37 (8.4)	65 (5.7)	1.39 (0.66 to 2.92)	0.32	0.90 (0.36 to 2.21)†	0.77
Ischaemic heart disease	61 (13.8)	109 (9.6)	1.50 (0.97 to 2.32)	0.06	1.07 (0.64 to 1.81)†	0.75
Chronic lung disease	41 (9.3)	72 (6.3)	1.25 (0.90 to 1.73)	0.17	1.15 (0.81 to 1.64)†	0.41
COPD	114 (25.8)	297 (26.2)	1.05 (0.50 to 1.38)	0.68	0.91 (0.68 to 1.23)†	0.51
Asthma	57 (12.9)	129 (11.4)	1.20 (0.85 to 1.70)	0.26	1.60 (1.08 to 2.38)†	0.02
Diabetes	78 (17.7)	171 (15.1)	1.19 (0.72 to 1.97)	0.43	1.00 (0.59 to 1.69)†	0.99
Cerebrovascular disease	41 (9.3)	75 (6.6)	1.37 (0.73 to 2.60)	0.27	1.00 (0.52 to 1.95)†	0.97
Cognitive impairment	13 (2.9)	30 (2.6)	0.81 (0.40 to 1.64)	0.52	0.60 (0.27 to 1.30)†	0.17
Immunosuppression	28 (6.3)	48 (4.2)	1.33 (0.88 to 2.01)	0.17	1.26 (0.81 to 1.96)†	0.28
Number of clinical risk factors						
0	148 (33.6)	440 (38.8)	Ref		Ref†	
1	160 (36.3)	442 (39.0)	1.28 (0.99 to 1.65)		1.10 (0.86 to 1.40)	
2	77 (17.5)	179 (15.8)	1.50 (1.01 to 2.22)	0.04*	1.16 (0.78 to 1.74)	0.22*
≥3	56 (12.7)	72 (6.4)	2.08 (1.106 to 3.94)		1.53 (0.80 to 2.94)	

p-values <0.05 are indicated in bold.

*P value for trend.

†Adjusted for age, sex, PPV23 receipt, chronic lung disease, ischaemic heart disease, chronic renal disease, liver disease and immunocompromise.

‡Adjusted for age.

aOR, adjusted OR; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; PPV23, pneumococcal polysaccharide vaccine.

Table 5 Association between severity of disease in single serotype 3 CAP patients compared with other single serotypes pneumococcal CAP

	Serotype 3 CAP N=441 (%)	Non-ST3 CAP N=1133 (%)	OR (95% CI)	P value	aOR (95% CI)	P value
CURB-65 score						
0–1 (low)	177/439 (40.3)	569/1127 (50.5)	Ref		Ref†	
2 (moderate)	140 (31.9)	321 (28.5)	1.47 (1.02 to 2.10)	0.02*	1.02 (0.70 to 1.45)	0.75
≥3 (high)	122 (27.8)	237 (21.0)	1.65 (1.15 to 2.38)		1.05 (0.76 to 1.44)	
Critical care admission	39 (8.8)	113 (10.0)	0.83 (0.52 to 1.33)	0.40	0.90 (0.52 to 1.57)‡	0.67
30-day mortality	37 (8.4)	65 (5.7)	1.72 (1.20 to 2.47)	0.01	1.32 (0.93 to 1.89)‡	0.11
30-day readmission	43/404 (10.6)	110/1066 (10.3)	1.07 (1.20 to 2.47)	0.78	0.92 (0.53 to 1.58)¶	0.72
Bacteraemic disease	12 (2.7)	149 (13.2)	0.39 (0.25 to 0.63)	<0.001	0.43 (0.27 to 0.68)**	0.001

p-values <0.05 are indicated in bold.

*P value for trend.

†Adjusted for age and chronic renal disease.

‡Adjusted for age and sex.

§Adjusted for age and CURB65.

¶Adjusted for age, sex and chronic renal disease.

**Adjusted for age and PPV23 receipt.

aOR, adjusted OR; CAP, community-acquired pneumonia; PPV23, pneumococcal polysaccharide vaccine.

the incidence of pneumococcal pneumonia pre-versus- post pandemic as the potential change in denominator values would tend towards an underestimate of postrestriction period incidence.

In conclusion, a large proportion of CAP continues to be caused by pneumococcal infection, with serotype 3 predominating and continuing to increase proportionately. We have not observed serotype 3 pneumonia to be more severe than other serotypes. Non-serotype 3 PCV13-vaccine type pneumonia does not appear to have increased significantly over the last 10 years. It is important for new pneumococcal vaccines to provide good protection against serotype 3 if adult pneumococcal pneumonia is to be reduced in future years, whether via direct or indirect protection.

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Competing interests WSL's institution received unrestricted investigator-initiated research funding from Pfizer for the conduct of this study (please see funding statement). WSL reports research funding from NIHR for a multicentre clinical trial of aspirin in community-acquired pneumonia in which WSL is a co-applicant. WSL is Deputy Chair of the Joint Committee of Vaccination and Immunisation (JCVI) (unpaid) and unpaid Chair of the NIHR Respiratory-Translational Research Centre's Acute Respiratory Infection National Strategy Research Group. CT participated in a CMV vaccine advisory board meeting in May 2022, unrelated to the topic of this paper. SE declares participation in a Virtual Advisory Board for a pneumococcal project organised by Sanofi Pasteur SA unrelated to the submitted work. The UK Health Security Agency (UKHSA) received monies from the University of Nottingham from an unrestricted grant from Pfizer for this work. The Vaccine Preventable Bacteria Section of UKHSA has received grants from GSK and Pfizer for investigator-led research unrelated to the current project. The UKHSA provides vaccine manufacturers (GlaxoSmithKline (GSK), MSD, Pfizer) with postmarketing surveillance reports on vaccine-preventable disease, including pneumococcal infections for which a cost recovery charge is made and which is unrelated to the submitted work. No other authors declare competing interests.

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REFERENCES

- Quan TP, Fawcett NJ, Wrightson JM, et al. Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998–2014. *Thorax* 2016;71:535–42.
- Jain S, Self WH, Wunderink RG, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med* 2015;373:415–27.
- Cillóniz C, Ewig S, Polverino E, et al. Community-acquired pneumonia in outpatients: aetiology and outcomes. *Eur Respir J* 2012;40:931–8.
- UK Health Security Agency. Chapter 25. pneumococcal. In: *Immunisation against infectious disease*. 2020. Available: <https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book>
- Berild JD, Winje BA, Vestreim DF, et al. A Systematic Review of Studies Published between 2016 and 2019 on the Effectiveness and Efficacy of Pneumococcal Vaccination on Pneumonia and Invasive Pneumococcal Disease in an Elderly Population. *Pathogens* 2020;9:259.
- Hanquet G, Krizova P, Dalby T, et al. Serotype Replacement after Introduction of 10-Valent and 13-Valent Pneumococcal Conjugate Vaccines in 10 Countries, Europe. *Emerg Infect Dis* 2022;28:137–8.
- Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. *Lancet Infect Dis* 2018;18:441–51.

- Dagan R, Patterson S, Juergens C, et al. Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: a randomized double-blind trial. *Clin Infect Dis* 2013;57:952–62.
- Horácio AN, Silva-Costa C, Lopes JP, et al. Serotype 3 Remains the Leading Cause of Invasive Pneumococcal Disease in Adults in Portugal (2012–2014) Despite Continued Reductions in Other 13-Valent Conjugate Vaccine Serotypes. *Front Microbiol* 2016;7:1616.
- van der Linden M, Falkenhofst G, Perniciaro S, et al. Effects of Infant Pneumococcal Conjugate Vaccination on Serotype Distribution in Invasive Pneumococcal Disease among Children and Adults in Germany. *PLoS One* 2015;10:e0131494.
- Andrews N, Kent A, Amin-Chowdhury Z, et al. Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: The indirect cohort design, 2006–2018. *Vaccine (Auckl)* 2019;37:4491–8.
- Weinberger DM, Harboe ZB, Sanders EAM, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clin Infect Dis* 2010;51:692–9.
- Ahl J, Littorin N, Forsgren A, et al. High incidence of septic shock caused by *Streptococcus pneumoniae* serotype 3—a retrospective epidemiological study. *BMC Infect Dis* 2013;13:492.
- Burgos J, Luján M, Larrosa MN, et al. Risk factors for respiratory failure in pneumococcal pneumonia: the importance of pneumococcal serotypes. *Eur Respir J* 2014;43:545–53.
- Platt H, Omole T, Cardona J, et al. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomised, double-blind, active comparator-controlled, multicentre, US-based trial. *Lancet Infect Dis* 2023;23:233–46.
- Campling J, Vyse A, Liu H-H, et al. A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom. *Expert Rev Vaccines* 2023;22:785–800.
- Lansbury L, Lawrence H, McKeever TM, et al. Pneumococcal serotypes and risk factors in adult community-acquired pneumonia 2018–20; a multicentre UK cohort study. *Lancet Reg Health Eur* 2024;37:100812.
- Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013–18. *Thorax* 2020;75:38–49.
- Eleutu SD, Sheppard CL, Rose S, et al. Re-validation and update of an extended-specificity multiplex assay for detection of *Streptococcus pneumoniae* capsular serotype/serogroup-specific antigen and cell-wall polysaccharide in urine specimens. *Access Microbiol* 2020;2:acmi000094.
- Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression and Survival Analysis*. New York, NY: Springer, 2001.
- Torres A, Blasi F, Dartois N, et al. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. *Thorax* 2015;70:984–9.
- Chow EJ, Uyeke TM, Chu HY. The effects of the COVID-19 pandemic on community respiratory virus activity. *Nat Rev Microbiol* 2023;21:195–210.
- Bertran M, D'Aeth J, Abdullahi F, et al. Invasive pneumococcal disease 3 years after introduction of a reduced 1 + 1 infant 13-valent pneumococcal conjugate vaccine immunisation schedule in England: a prospective national observational surveillance study. *Lancet Infect Dis* 2024;24:546–56.
- Neal EFG, Chan J, Nguyen CD, et al. Factors associated with pneumococcal nasopharyngeal carriage: A systematic review. *PLOS Glob Public Health* 2022;2:e0000327.
- Wolter N, Tempia S, Cohen C, et al. High nasopharyngeal pneumococcal density, increased by viral coinfection, is associated with invasive pneumococcal pneumonia. *J Infect Dis* 2014;210:1649–57.
- Yang Z, Bou-Attoun S, Gerver S, et al. Sustained increases in antibiotic prescriptions per primary care consultation for upper respiratory tract infections in England during the COVID-19 pandemic. *JAC Antimicrob Resist* 2023;5:slad012.
- Vestesson E, De Corte K, Chappell P, et al. Antibiotic prescribing in remote versus face-to-face consultations for acute respiratory infections in primary care in England: an observational study using target maximum likelihood estimation. *EclinMed* 2023;4:102245.
- Forstner C, Kolditz M, Kesselmeier M, et al. Pneumococcal conjugate serotype distribution and predominance of serotype 3 in German adults with community-acquired pneumonia. *Vaccine (Auckl)* 2020;38:1129–36.
- Torres A, Menéndez R, España PP, et al. The Evolution and Distribution of Pneumococcal Serotypes in Adults Hospitalized With Community-Acquired Pneumonia in Spain Using a Serotype-Specific Urinary Antigen Detection Test: The CAPA Study, 2011–2018. *Clin Infect Dis* 2021;73:1075–85.
- Silva-Costa C, Gomes-Silva J, Santos A, et al. Adult non-invasive pneumococcal pneumonia in Portugal is dominated by serotype 3 and non-PCV13 serotypes 3-years after near universal PCV13 use in children. *Front Public Health* 2023;11:1279656.
- Hyams C, Lahuerta M, Theilacker C, et al. Surveillance of pneumococcal serotypes in adults hospitalised with acute lower respiratory tract infection in Bristol, UK. *Vaccine (Auckl)* 2024;42:1599–607.
- Silva-Costa C, Gomes-Silva J, Pinho MD, et al. Continued Vaccine Breakthrough Cases of Serotype 3 Complicated Pneumonia in Vaccinated Children, Portugal (2016–2019). *icrobiol Spectr* 2022;10:10177–22.
- Africano HF, Serrano-Mayorga CC, Ramirez-Valbuena PC, et al. Major Adverse Cardiovascular Events During Invasive Pneumococcal Disease Are Serotype Dependent. *Clin Infect Dis* 2021;72:e711–9.
- Gutiérrez F, Masía M, Mirete C, et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. *J Infect* 2006;53:166–74.
- Wagenvoort GHJ, Sanders EAM, Vlamincx BJ, et al. Sex differences in invasive pneumococcal disease and the impact of pneumococcal conjugate vaccination in the Netherlands, 2004 to 2015. *Euro Surveill* 2017;22:30481:10.
- Office for National Statistics (ONS). ONS website, article, profile of the older population living in england and wales in 2021 and changes since 2011. 2023. Available: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/profileoftheolderpopulationlivinginenglandandwalesin2021andchangesince2011/2023-04-03>
- Sings HL, De Wals P, Gessner BD, et al. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Invasive Disease Caused by Serotype 3 in Children: A Systematic Review and Meta-analysis of Observational Studies. *Clin Infect Dis* 2019;68:2135–43.
- Tiley KS, Ratcliffe H, Voysey M, et al. Nasopharyngeal Carriage of *Pneumococcus* in Children in England up to 10 Years After 13-Valent Pneumococcal Conjugate Vaccine Introduction: Persistence of Serotypes 3 and 19A and Emergence of 7C. *J Infect Dis* 2023;227:610–21.
- Ladhani SN, Andrews N, Ramsay ME. Summary of evidence to reduce the two-dose infant priming schedule to a single dose of the 13-valent pneumococcal conjugate vaccine in the national immunisation programme in the UK. *Lancet Infect Dis* 2021;21:e93–102.
- Office for National Statistics (ONS). ONS website, statistical bulletin, national population projections: 2021-based interim. 2024 Available: <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/bulletins/nationalpopulationprojections/2021basedinterim>
- Kidney Research UK. Kidney disease: a uk public health emergency. 2023. Available: https://www.kidneyresearchuk.org/wp-content/uploads/2023/06/Economics-of-Kidney-Disease-full-report_accessible.pdf#6

Novos caminhos de gestão para o acompanhamento de doentes com apneia do sono tratados com CPAP, incluindo medicina digital e telemonitorização multimodal

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RESUMO

Contexto: O número crescente de doentes diagnosticados com apneia obstrutiva do sono (OSA) e tratados com pressão positiva contínua nas vias aéreas (CPAP) a longo prazo sobrecarrega os caminhos convencionais de acompanhamento. Novas abordagens na gestão de doentes tratados com CPAP são necessárias para equilibrar o monitoramento remoto por meio de tecnologias digitais e os contatos presenciais entre doentes e profissionais de saúde.

Objetivo: Focando na reestruturação dos caminhos de cuidado para doentes tratados com CPAP, com ênfase em plataformas de telemonitorização, o objetivo foi revisar evidências sobre como ferramentas de medicina digital e inteligência artificial (IA) estão facilitando o fenotipagem e triagem de doentes, estratificação de risco e alocação de recursos entre vários profissionais de saúde para um acompanhamento ideal.

Fenotipagem: A OSA é uma condição heterogênea com fenótipos diversos, que diferem em sintomas, comorbidades, características demográficas, estilo de vida e contexto socioeconômico. Esses diferentes fenótipos estão associados a padrões distintos de adesão ao CPAP e prognósticos a longo prazo. Essa diversidade exige uma maior pluralidade nos caminhos de gestão, com diferentes tipos e níveis de suporte para garantir adesão ao tratamento e redução de risco para doentes, enquanto alivia a carga sobre os serviços de saúde.

Clínicas de cuidados integrados para doentes de alto risco: Explora-se o papel das clínicas integradas de OSA, particularmente para o manejo de doentes de alto risco, com baixa adesão e progressão de comorbidades. Nessas clínicas, equipas multidisciplinares podem propor gerenciamento de comorbidades e usar dispositivos conectados para monitoramento a longo prazo da atividade física, junto com o monitoramento remoto de CPAP. Caminhos de gestão remota: São considerados os prós e contras dos caminhos de gestão remota para substituir visitas de acompanhamento presencial, incluindo a necessidade de reavaliar as políticas de reembolso dos dispositivos CPAP em alguns países. Enquanto o monitoramento remoto de CPAP tornou-se a pedra angular do acompanhamento, fornecendo informações sobre adesão e eficácia, o processamento de alertas precisa ser aprimorado, especialmente em relação a alterações de máscara e detecção precoce de falhas do CPAP.

Desafios: A implementação do monitoramento CPAP, bem como sua extensão para monitoramento multimodal, pode apresentar desafios que ainda precisam ser abordados (ex.: acesso a cuidados digitais). A extensão e os componentes do acompanhamento remoto devem ser adaptados a cada fenótipo específico de OSA. São dados exemplos de fenótipos específicos de doentes (ex.: insônia com OSA) com requisitos específicos de acompanhamento, para os quais apenas o monitoramento remoto (mesmo multimodal) tem limitações e exige a intervenção de especialistas do sono e/ou colegas de outras disciplinas.

Conclusão: Caminhos de acompanhamento combinados, apropriados e personalizados, que incluem monito-

ramento digital e presencial, oferecem vantagens tanto para os doentes com OSA quanto para os serviços de saúde.

INTRODUCTION AND SCOPE

Obstructive sleep apnoea (OSA) is one of the most frequent chronic diseases (affecting nearly one billion people worldwide) and its prevalence will continue to increase owing to the overall ageing of the population in many countries, exacerbated by the obesity and diabetes epidemics.^{1,2} As an illustration, the annual number of patients treated for sleep apnoea increased by 610% in Finland between 1996 and 2018.³ There is no doubt that this trend is generalisable to all other developed countries. The ensuing pressure on healthcare services and the economic burden caused by sleep apnoea requires urgent reorganisation of care pathways. The availability and uptake of healthcare services according to the needs of each patient should ultimately lead to better outcomes for patients and reduce the societal cost per patient with OSA.⁴

Most patients with OSA are managed in an ambulatory care setting, which provides opportunities for care supported by digital medicine. There are active databases of the long-term follow-up of millions of OSA patients treated by continuous positive airway pressure (CPAP), the primary therapy for OSA.⁵⁻⁷ During the COVID-19 pandemic, sleep medicine services transitioned nearly completely to virtual care. In the USA and some European countries, policy-makers endorsed the fast-track approval of video-visit reimbursements. There has been intense activity towards implementing remote patient monitoring technologies.⁸ Population-level digital healthcare systems for other chronic diseases (such as chronic kidney disease) are now in place in several countries and have the potential to reduce fragmented clinical care and optimise follow-up management.⁹ Nevertheless, there is a pressing need to create new outpatient models of care such as personalised care, longitudinal multidimensional remote monitoring with wearable devices and machine learning-derived clinical decision tools as routine practical approaches that actively impact patient care.⁸

Compared with broader reviews addressing personalised care in OSA,¹⁰⁻¹² the distinctiveness of this review is that it focuses on the reshaping of the management of care pathways of CPAP-treated patients with special emphasis on telemonitoring platforms. We share our vision on how digital medicine and artificial intelligence tools are facilitating patient phenotyping and triage, risk stratification and the allocation of resources between the various healthcare professionals for an optimal follow-up of CPAP-treated patients.

METHODOLOGY

References for this review were identified by searches of PubMed and Cochrane databases be-



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tween January 2000 and December 2024, using the following terms:

“Sleep Apnea Syndromes” [MeSH] OR “Sleep Disordered Breathing”) AND “continuous positive airway pressure” [MeSH] AND Telemonitoring [Text Word]. Additionally, we extended our research to “Sleep Apnea Syndromes” [MeSH] OR “Sleep Disordered Breathing”) AND (“critical pathways” [MeSH] OR “Care Pathway” [Text Word]).

Articles in English and French were considered. We also searched the reference lists of retrieved articles. We then selected the most relevant references, paying particular attention to studies within the past 10 years (although we retained some older studies for their importance).

HARNESSING A COMBINATION OF DIGITAL AND CONVENTIONAL MODELS OF CARE FOR CPAP-TREATED PATIENTS

Conventional current care pathways rely heavily on devices managing the upper airway obstruction that causes OSA prominently with CPAP. In that case, new management pathways will intend to offer more personalised and innovative treatment solutions, including combination therapies and digital health tools (eg, telemonitoring, visualisation dashboard) aiming to improve adherence, comfort and overall effectiveness (figure 1).

The first step to achieve precision and personalised care for patients with OSA¹² is to design new management pathways that provide a holistic solution that acknowledges the extreme heterogeneity of OSA phenotypes and can deliver integrated care beyond the conventional ‘one-size-fits-all’ CPAP approach.

The prescription of CPAP alone in the absence of monitoring of its use and effectiveness is inadequate for many patients¹³ and is associated with high rates of CPAP termination.¹⁴ The new management models will allow easier access to different OSA primary therapies and personalised follow-up procedures covering clinical scenarios tailored to individual risk profiles. Such a strategy requires a dedicated multidisciplinary care team including home-care providers, and non-physician caregivers¹⁵ supervised by respiratory/sleep physicians¹⁶ and assisted by remote monitoring platforms. The latter allows relevant information to be shared among all caregivers and with patients.

Multidimensional phenotyping and risk stratification

‘Sleep apnoea’ is a generic diagnosis incorporating heterogeneous and diverse phenotypes.^{13–17} Several cluster analyses have tried to characterise the different OSA subgroups that are essentially separated by symptoms (from minimally symptomatic patients with few symptoms and complaints at diagnosis to those with disabling

daytime sleepiness), the burden of comorbidities and the context of occurrence including age, sex, obesity and lifestyle (eg, low physical activity and unhealthy diet).^{18–20} Different combinations of comorbidities are associated with different CPAP adherence patterns¹⁴ and differing long-term prognoses. Patients with severe sleepiness²¹ or cardiovascular and/or metabolic diseases represent populations at particularly high risk of long-term cardiovascular events and are also characterised by differences in trajectories of CPAP adherence.²² Also, socioeconomic and environmental determinants of health, such as diet, family circumstances and couple structure are crucial contextual factors predicting long-term prognosis and adherence to therapies.²³ This diversity in OSA subgroups (ie, in terms of phenotypes and endotypes) should translate into personalised management pathways, each designed for different patient subtypes (figure 1). From that perspective, and for patients with an indication of CPAP treatment, different levels of support to improve treatment adherence and efficient risk reduction should be offered.^{24–26} If the potential of these approaches is obvious, their implementation in clinical routine is still lacking. There is an urgent need for personalised treatment strategies including follow-up, intending to progress from a ‘one-size-fits-all’ to a ‘tailored-therapy’ approach.²⁶

Long-term CPAP adherence remains an issue in patients with OSA as overall CPAP termination rates can reach nearly 50% at 3 years after CPAP initiation.¹⁴ Therapy termination rates are highest in the young and elderly patient bands and comorbidities have an important influence on long-term CPAP continuation. Other factors (psychological, couple profile, socioeconomic status, access to care and cultural background) should also be better acknowledged and included in extended phenotyping and tailored interventions.²³

The grade of OSA severity is currently mostly based on the apnoea hypopnoea index (AHI), however, this metric is now considered as being poorly related to outcomes, in particular, concerning cardiovascular events and adherence to treatment.²⁷ The amount of nocturnal exposure to hypoxia, called the hypoxic burden (HB), and indices of sympathetic activation related to OSA have been proposed to compensate for the shortcomings of the AHI metric and to better reflect cardiovascular prognosis.^{28–31} These indices could be derived from type I to type III sleep studies and may represent indicators of which calculation could be easily automated and embedded in diagnostic tools. Other markers, derived from types I to II sleep studies,³² reflecting the impact of OSA on sleep quality and architecture have also been investigated, and have also been described as being associated with health outcomes.³³ Despite their potential considerable interest in risk stratification, this new

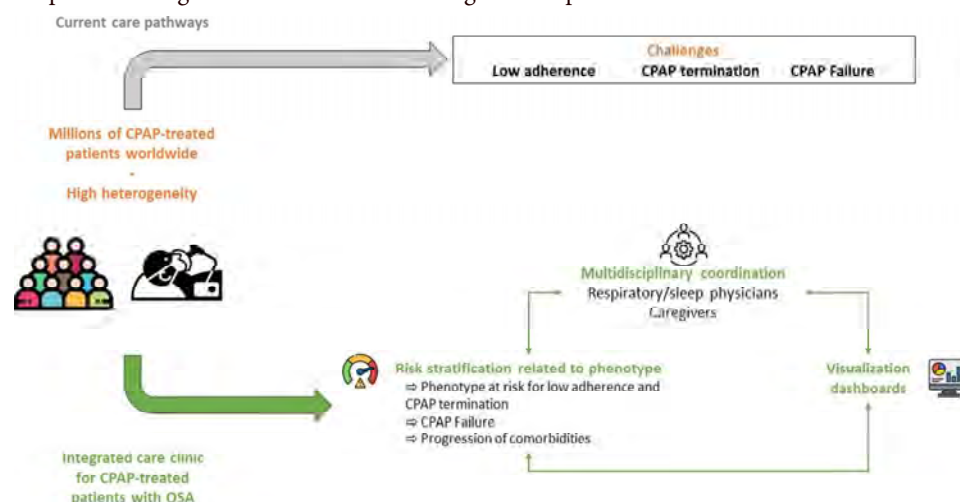


Figure 1 Implementing new management pathways for patients with obstructive sleep apnoea treated by CPAP. The organisational and economic burden caused by ever-increasing numbers of patients with OSA on CPAP treatment requires the reorganisation of healthcare services, in particular by incorporating risk prediction of poor CPAP adherence and CPAP termination. Conventional current care pathways rely heavily on devices managing the upper airway obstruction that causes OSA prominently with CPAP, with regular in-person meetings during treatment follow-up. New management pathways will offer more personalised and innovative treatment solutions and will rely on digital health tools aiming to improve adherence, comfort and overall effectiveness. CPAP, continuous positive airway pressure; OSA, obstructive sleep apnoea.

approach requires several refinements (regarding generalisation of the findings and capabilities) before being included in clinical prediction models. To date, these novel parameters have essentially been investigated retrospectively in selected populations (community sample cohorts) or subgroups of participants in clinical trials, implicating low OSA severity or selection biases. Nowadays, it is mandatory to conduct prospective validations in clinical databases of multimorbid OSA patients with various medication regimens before implementing these indices in routine clinical practice. In the future, unambiguous and reproducible definitions of these new parameters (beyond AHI), shared computational algorithms and combinations of indices reflecting HB and cardiovascular reactivity are desirable to achieve robustness in the prediction of outcomes.²⁹ This field is promising and rapidly evolving but needs consolidation of knowledge.

There is a need for the development of 'stratification' tools facilitating risk assessment and the identification of appropriate individualised (risk-based) surveillance strategies. Applying artificial intelligence and machine learning to large OSA databases could reveal latent associations between phenotypes, HB and sympathetic activation, socioeconomic characteristics, behaviours and patient engagement in therapy, and health outcomes. There is already a move to implement some of these concepts in routine management pathways. They may be included in step-by-step analytical approaches and reasoning to distinguish between phenotypes, or used in easy-to-identify risk factors (specific targets for interventions) or subgroups at risk of low CPAP adherence. We have recently demonstrated³⁴ that capturing patient-reported outcomes using digital solutions during the course of treatment has the potential to enhance long-term patient outcomes by providing actionable insights. In fact, self-reported sleepiness and its response to therapy are associated with CPAP usage.³⁴

Alternative follow-up pathways

With digital support, not all patients will need specialist follow-up. There are several factors supporting the management of OSA in a primary care setting,^{35–39} these include the difficulties in access to specialists and the lack of clarity around the roles of the different healthcare providers. After initial multidimensional phenotyping and risk stratification by specialists, the follow-up of low and medium-risk patients^{14 40} could be referred to general practitioners (GPs) for long-term follow-up. Similarly, easy-to-manage

symptomatic patients, with high treatment expectancies (ie, patients who are highly symptomatic at diagnosis in terms of sleepiness, fatigue and diminution in quality of life, but who demonstrate good early adherence to CPAP) might be referred to GPs working in close networks with OSA integrated care clinics, unless there is another indication requiring referral to a respiratory physician, including, but not restricted to, suspicion of obesity hypoventilation syndrome, overlap syndrome or comorbid OSA and asthma. Nevertheless, we recently observed a higher therapy termination rate when CPAP was initiated by GPs versus specialists.⁴¹ For CPAP initiation (as opposed to follow-up), it is possible that GPs have less time per appointment to spend with patients than specialists and a lack of knowledge or appropriate training. Management of OSA in many countries is currently shared between sleep specialists, respiratory physicians, cardiologists, Ear, Nose and Throats physicians and GPs. Thus, although primary care models of OSA care and service delivery will differ between countries, successful initiation and efficacy of CPAP therapy require strong support and established networks with access to existing specialist sleep services.

In contrast, more difficult-to-manage phenotypes like comorbid insomnia and sleep apnoea (COMISA) that necessitate multifaceted treatment approaches (including cognitive behavioural therapies⁴²) need to be subject to specific multidisciplinary interventions supported by digital remote monitoring platforms. Also, the frequently encountered minimally symptomatic OSA phenotype with an accumulation of multiple cardiometabolic comorbidities and expected poor CPAP adherence¹⁴ should benefit from both lifestyle interventions and close follow-up via a CPAP device linked to a remote monitoring platform. Access to these strategies should be supported by improved dashboards (figure 2), allowing physicians to access all the information required for efficient CPAP management in a single, synthetic view. We, therefore, suggest that improved visualisation dashboards should combine: (1) patient phenotype characterisation, including patients' comorbidities and their treatment, symptoms (both OSA-related symptoms and symptoms indicative of comorbid sleep disorders), alerts on factors (eg, comorbidities) that may favour CPAP failure and (2) multimodal and multidimensional CPAP treatment follow-up parameters, including questionnaires for the evaluation and longitudinal follow-up of patients reported outcomes and telehealth parameters (eg, physical activity parameters and blood pressure

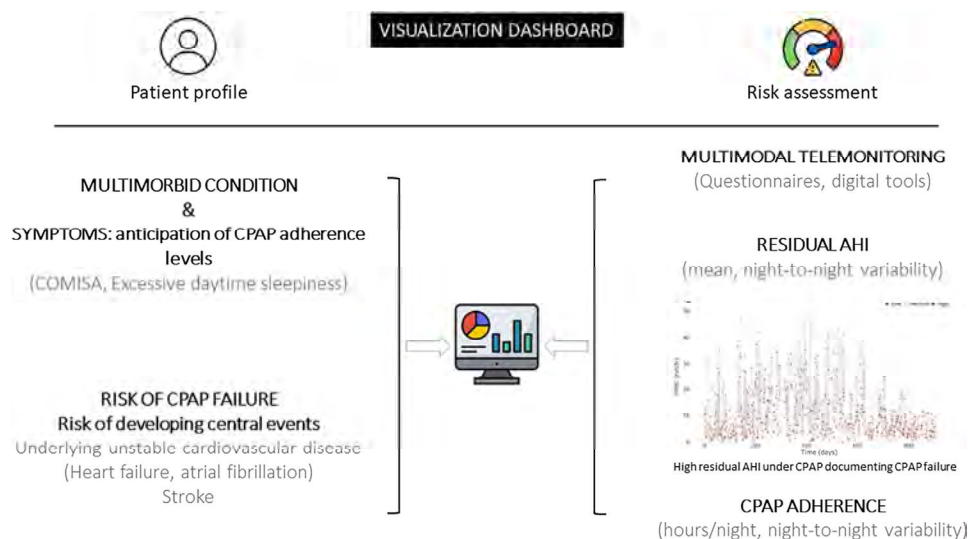


Figure 2 Dashboards to visually summarise patient characteristics. Caregivers should be better informed of the patient's home and clinical situation through readily accessible dashboards that should combine: (1) patient phenotype characterisation, including patients' comorbidities and their treatment, symptoms (both OSA-related symptoms and symptoms indicative of comorbid sleep disorders), alerts on factors (eg, comorbidities) that may favour CPAP failure and (2) multimodal and multidimensional CPAP treatment follow-up parameters, including questionnaires for the evaluation and longitudinal follow-up of patients reported outcomes and telehealth parameters (eg, physical activity parameters, blood pressure ambulatory measurements results) and reliable parameters issued from CPAP remote monitoring platforms including residual AHI and CPAP adherence. Modified from Midelet *et al.*⁴⁵ AHI, Apnoea Hypopnoea Index; COMISA, comorbid insomnia and sleep apnoea; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnoea.

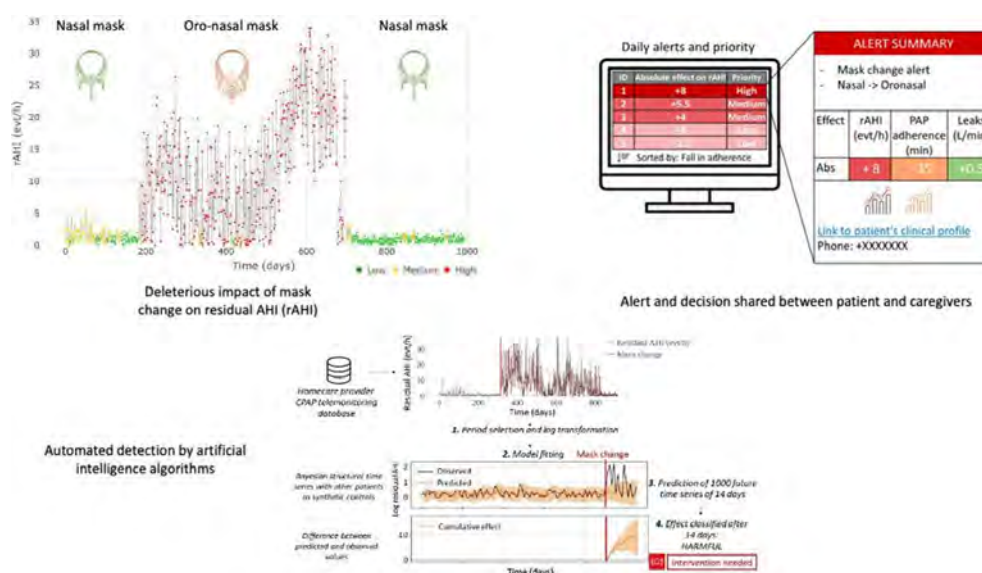


Figure 3 Developing the full potential of multimodal remote monitoring platforms. For example, for the deleterious impact of a mask change. Replacing masks is one of the most frequent technical procedures in long-term CPAP treatment. Oro-nasal masks are associated with a higher residual AHI such that a switch from a nasal pillow or nasal mask to an oro-nasal mask might trigger a higher residual AHI and apparent CPAP failure. This situation occurs for more than 10% of CPAP-treated patients but is currently poorly detected in routine CPAP follow-up. Bayesian structural time series with synthetic controls allows to automatically classify the impact of mask changes on rAHI, informing patients and caregivers. Modified from Midelet *et al.*^{44,45} AHI, Apnoea Hypopnoea Index; CPAP, continuous positive airway pressure.

ambulatory measurements results), and reliable parameters issued from CPAP remote monitoring platforms including residual AHI (rAHI) and CPAP adherence. Innovative analytics, including artificial intelligence, may allow the integration of variability parameters and automated alarms (see below for a dedicated paragraph) (figure 3).^{43–45}

Establishing an integrated care clinic for CPAP-treated patients with OSA

The OSA clinic should be coordinated by respiratory/sleep physicians with a special interest in the management of complex OSA patients. First, the development of an initial standardised OSA evaluation protocol and dashboard will allow the stratification of patients according to their risks of low adherence, CPAP failure and progression of comorbidities (figure 2). The visualisation dashboards¹² should inform caregivers of the patient's clinical phenotype and highlight subgroups with a high risk of poor adherence (eg, a patient with COMISA), high risk of CPAP failure (underlying unstable cardiovascular disease such as cardiac failure or atrial fibrillation making the patient prone to developing central events) and multimorbid conditions requiring specific follow-up and multimodal telemonitoring. The patient profile should be completed on the dashboard by a presentation of the specific metrics of CPAP adherence, rAHI, lifestyle indicators (sleep duration, number of steps) and home self-measured blood pressure.

OSA is a heterogeneous condition with various risk profiles, but a consensual definition of risk levels is still lacking. Designing personalised care pathways requires a multidimensional assessment of OSA-associated risk with three main dimensions, that may help orientate patients to either GPs or specialists for CPAP follow-up:

- **Comorbidities:** Patients suffering from comorbidities that may complicate the interpretation of diagnostic tests (ie, a suspected comorbid sleep disorder other than SA, chronic obstructive pulmonary disease or cardiac insufficiency) or CPAP adherence should be managed by specialists.
- **Cardiovascular risk and risk of incident cardiovascular events:** Cardiovascular risk assessment and re-evaluation must be integrated into OSA care. We acknowledge that there is currently no clear consensus on risk stratification and level of risks in OSA patients. Classification tools (such as BAVENO classification⁴⁰) and calculation automation of novel metrics of OSA

severity,⁴⁶ once validated in prospective cohorts, may represent interesting tools to stratify the risk in this population.

- **Risk of CPAP failure:** Patients with a high risk of CPAP failure or discontinuation should be managed by specialists.^{47,48}

In summary, patients with an at-risk profile would be requested to attend the integrated OSA outpatient clinic. On the other hand, specialist advice and guidance should be offered to primary care providers looking after patients with low risk.

In the outpatient OSA clinic for at-risk patients, three distinct main topics need to be managed:

1. Technical CPAP follow-up (figure 4) should be shared with non-physician providers including specialised nurses and/or home care providers. The interaction between physicians and non-physician providers will be centred on the now well-established CPAP remote monitoring platforms (see description in this review). A recent RCT involving alternative care providers (ACP)⁴⁹ reported greater improvements in sleepiness and quality of life in the ACP arm, probably owing to more time dedicated by ACPs to informing and managing patients, compared with less caregiver-patient exchanges in the sleep physician's arm.
2. Comorbidity management: As at least half of the OSA population is obese and/or multimorbid, the clinic should include input from diabetologists and cardiologists via multidisciplinary team meetings. This organisation provides an opportunity for medicine optimisation as well as addressing risk factors of disease progression. Again, non-physician providers will be included in implementing and conducting lifestyle interventions in the nutrition and physical activity domains, supported or not by telehealth.⁵⁰
3. Long-term non-intrusive monitoring: Information collected during face-to-face visits poorly reflects everyday lifestyle behaviours and the impact of follow-up on the progression and control of comorbidities. There is room for extending the collection of real-life data on daily activities and physiological parameters via smartphones and/or wearable connected devices.

ARCHITECTURE OF A REMOTE MANAGEMENT PATHWAY FOR ROUTINE CLINICAL USE

There are millions of CPAP-treated patients with OSA on active long-term care. For example, in Finland, in the 10-year period

from 2010 to 2019, the number of new patients with sleep apnoea increased from 89 to 388 per 100 000 inhabitants (439%).³ The resources needed to follow up such large numbers of patients are immense. No clear consensus is available regarding the number and the timing of face-to-face or virtual visits necessary to achieve the best outcomes. Consequently, there are huge variations between European countries in the number of follow-up visits required for CPAP treatment reimbursement. Stringent models in France and Belgium^{14 51} require a strict follow-up of patients with multiple visits at CPAP initiation and then mandatory annual follow-up visits. French national recommendations for reimbursement are CPAP usage of >4 hours/night, and reimbursement rates progressively decrease when there is very low adherence to CPAP. However, CPAP delivery and reimbursement can continue when adherence is between 2 and 4 hours/night pending additional patient education and coaching. Strict follow-up of all patients through in-person visits to encourage treatment adherence and resolve problems is unsustainable. Consequently, new care and follow-up strategies are progressively being implemented supported by digital medicine and remote monitoring platforms. This reshaping of care pathways requires careful monitoring of their impact on outcomes, cost-effectiveness and if necessary, the modification of reimbursement policies (figure 4).

The first pillar of remote management pathways for CPAP-treated patients with OSA is follow-up by virtual consultation, either by telephone or videoconferencing.⁵² The 2019 COVID-19 pandemic accelerated the adoption of such virtual care strategies. A recent review and meta-analysis incorporating 12 studies (n=1823 adults with OSA)⁵³ showed that virtual care was as effective as in-person consultations for improving subjective sleepiness in patients with OSA treated with CPAP. The authors further suggested that remote management of patients using CPAP should be available as an alternative care strategy to in-person follow-up, depending on the patient's preference.⁵³

The second pillar of remote management pathways is telemonitoring of the CPAP treatment.⁵⁴ CPAP remote monitoring has already transformed the management of OSA and produced a massive amount of data. Accumulated CPAP data provide valuable and objective information regarding patient treatment adherence and rAHI.⁵⁴ Every night CPAP devices transmit detailed data of objective usage (hours per night) and rAHI quantifying the reduction of abnormal events during sleep. Embedded in dedicated virtual platforms, telemonitoring has transformed the way patients are followed.

CPAP adherence and remote monitoring platforms

The improvement in symptoms and long-term outcomes in individuals with OSA are closely related to CPAP adherence.²³ CPAP is highly effective in improving patient-reported outcome measures and cardiovascular risk in adherent patients.²³ Currently, 1.6 million individuals with OSA are treated with CPAP in France. Data from the French National Medico-Administrative Database shows that mortality is increased in individuals who terminate CPAP therapy compared with those who continue.⁵¹ However, nearly 50% stop CPAP therapy in the first 3 years after initiation. These figures are based on data from an exhaustive nationwide database including half a million OSA patients initiated on CPAP in France in the years 2015 and 2016.¹⁴ Remote CPAP monitoring is acknowledged as being effective in improving CPAP adherence,^{55,56} without increasing costs.⁵³ CPAP telemonitoring provides dynamic trajectories of CPAP adherence⁴³ allowing early intervention and support via patient-engagement tools. It has been demonstrated that automated patient feedback text messaging⁵⁷ or active patient engagement technology using smartphone applications⁵⁸ is increasing adherence in patients with OSA by about 1 hour per night, which is twice the minimum clinically important difference of 30 min. The early identification of patients with adherence problems also increased clinic attendance for OSA re-evaluation.

CPAP efficacy and remote monitoring platforms

An elevated or variable rAHI reflects CPAP treatment failure.^{45 48} High rAHI and large rAHI variability are associated with underlying cardiometabolic comorbidities, some medications, or poorly adapted or defective CPAP equipment including mask type and settings. The detection and surveillance of high rAHI via CPAP remote monitoring allows an adaption of drug dosage or withdrawal, reappraisal and treatment of unstable comorbidities, and if needed a change in the type of mask. This is relevant not only in long-term follow-up care, but it is now well established that abrupt elevations in the rAHI are triggered by exacerbation of underlying cardiovascular comorbidities or incident cardiovascular events indicating a need for reassessment and referral to cardiology colleagues.^{58 59} These clinical situations can generate persistent or treatment-emergent central sleep apnoea (CSA) leading to a reduction in CPAP adherence. Switching from CPAP to adaptive servoventilation is the appropriate clinical decision to control residual events and is associated with improvements in adherence.^{60 61}

Alert management

The organisational challenge is to manage the alerts generated by the telemonitoring platform on an ongoing basis. The urgency and

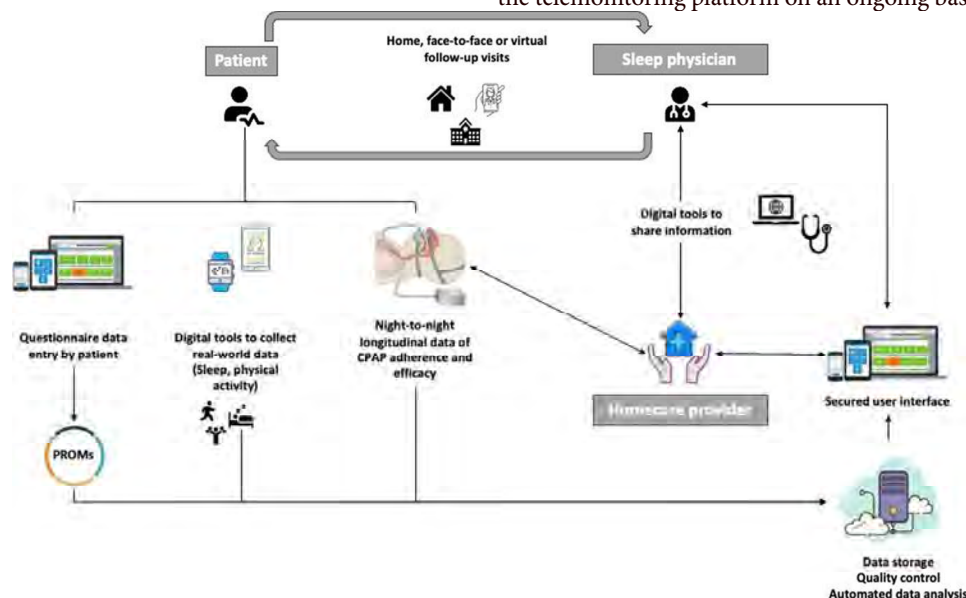


Figure 4 An integrated care clinic for patients with OSA treated by CPAP. The OSA clinic should be coordinated by respiratory/sleep physicians and management tasks shared with non-physician providers including specialised nurses or home care providers. CPAP, continuous positive airway pressure; OSA, obstructive sleep apnoea; PROMs, patient-reported outcome measures.

allocation of these alerts to the appropriate caregiver need to be managed by automated systems. Such systems are currently being developed or being validated. A major goal is to automatically differentiate between technical alerts linked to equipment and masks, and alerts requiring specialist medical intervention. This is essential so as to avoid overloading the physician's workload (Figure 3).

Replacing masks is one of the most frequent technical procedures in the long-term CPAP care of the patient.⁶² The mean number of 2.1 resupply shipments per patient corresponds to millions of interventions per year.⁶² Oro-nasal masks are associated with a higher rAHI and a switch from a nasal pillow or nasal mask might be the trigger for sudden high rAHI and partial CPAP failure. This situation occurs in more than 10% of CPAP-treated patients but is currently poorly detected in routine CPAP follow-up.⁴⁴ Recently, we proposed a Bayesian structural time series with synthetic controls to automatically classify the impact of mask changes on rAHI (figure 3).⁴⁴ This end-to-end method of automatically classifying harmful technical interventions might be extended to automate the measurement of the impact of changes in CPAP pressure settings or changes in the CPAP device model or brand.⁶³

The second clinically relevant potential of CPAP remote monitoring is the early detection of acute health events essentially related to exacerbations of cardiovascular OSA-related comorbidities.^{58,59} CPAP telemonitoring provides typical 'digital signatures'⁶⁴ that are currently underused for detecting deterioration in cardiac function or the onset of arrhythmias.⁶⁵

Multimodal remote monitoring platforms

'Life's Simple 7' (a prescription for good health developed by the AHA) characterised cardiovascular health based on seven domains: smoking, diet, physical activity, body mass index, blood pressure, cholesterol and fasting glucose. This metric of risk prediction has been recently updated to 'Life's Essential 8' by the addition of sleep health.⁶⁶ The burden of OSA-related cardiometabolic comorbidities is high in patients with sleep apnoea and requires integrated risk reduction. Beyond CPAP treatment therapies, blood pressure control with appropriate medications and lifestyle interventions with physical activity and weight loss management are recommended. In addition to remote monitoring of CPAP adherence, multimodal telemonitoring, by non-intrusively collecting real-life data on daily activities and comorbidity-related parameters via smartphones⁶⁷ or connected wearable devices^{68–70} may also have a clear impact on OSA management. In a randomised controlled trial, multimodal telemonitoring including CPAP remote monitoring combined with wearables measuring blood pressure and number of steps conducted in patients with OSA at high cardiovascular risk improved CPAP adherence and patient-centred outcomes (ie, daytime sleepiness and quality of life).⁷⁰ Such an impact was not observed in patients with OSA at low cardiovascular risk.⁷¹ In a recent randomised controlled trial recruiting patients with obesity and OSA treated by CPAP (168 patients recruited in 16 centres in Japan), the multimodal telemonitoring group was encouraged by physicians to reduce their body weight (BW), after sharing the remotely obtained data on BW, blood pressure and step count.⁷² A greater percentage of BW reduction ($\geq 3\%$) was observed in the multimodal telemonitoring group compared with the usual CPAP telemonitoring group.⁷²

Challenges and pitfalls of remote monitoring platforms

Although having a high potential to improve CPAP adherence and integrated OSA care, the development and implementation of remote management pathways face several pitfalls that remain to be resolved. One major barrier is inequality in access, disadvantaging certain sectors of the population (ie, 'The digital divide')⁷³ due to technical, cultural and financial obstacles. Another major concern is to implement and maintain high quality and standardised data handling.⁵⁴ There is a lack of standardisation among the indicators provided by different CPAP brands impacting the validity of information available to physicians.⁵⁴ Thus, rules need to be proposed by scientific societies to increase homogeneity in reported

CPAP efficacy parameters. Another problem requiring attention is the differentiation between missing CPAP values and faults in data transmission. To avoid biases in computation, CPAP data management and processing should be conducted rigorously with these points in mind. CPAP remote monitoring data contain a wealth of original information that is currently underused in routine practice and research. Open access and data sharing among specialists worldwide needs to be encouraged and facilitated to compare different health systems and to permit strategies that use artificial intelligence to be employed in the field of CPAP follow-up care pathways. Furthermore, the wearable connected devices used for multimodal telemonitoring of health-related parameters need to be properly evaluated and validated.⁷⁴ Finally, many regulatory aspects regarding data privacy and healthcare regulations still need to be resolved with a focus on defining the data of greatest interest for diagnostic and follow-up purposes.

CPAP monitoring platforms provide a true opportunity for the development of shared decision-making in the field⁷⁵ by giving patients access to the processing of their own data and allowing them and their caregivers to make informed decisions regarding lifestyle changes that promote better health. Digital platforms can also be used to capture patient-reported outcomes (figure 4).³⁴

CARE TRAJECTORIES ILLUSTRATING THE FUNCTIONING OF NEW CPAP MANAGEMENT PATHWAYS IN ROUTINE CLINICAL SETTINGS

Symptomatic sleepy OSA free of comorbidities or with well-controlled comorbidities

In these patients, a major improvement in symptoms is expected to be associated with lowering of rAHI as there are no associated conditions susceptible to generate treatment emergent CSA. The anticipated outcomes can be readily checked after 1–3 months of treatment using a combination of the remote CPAP monitoring platform and an in-person or virtual visit (depending on the patient's preference). This visit would ideally be conducted by a physician but might be delegated to a non-physician caregiver if the remote monitoring platform conveys satisfactory results, that is, low rAHI with low rAHI variability in the context of at least 4 hours of daily usage of CPAP and controlled leaks. These patients with a lower risk of CPAP termination and complications would continue with standard care through their primary care provider unless there was another indication for referral to a respiratory/sleep physician. This 'straightforward' follow-up mode is suitable for the majority of patients with OSA and should allow reallocation of human resources to more complex and at-risk clinical situations.³

Comorbid insomnia and obstructive sleep apnoea

This clinical phenotype⁷⁶ is one of the most frequent but remains insufficiently recognised in current practice. These patients not only exhibit disabling symptoms related to the two interrelated sleep disorders but are also at high risk of poor adherence and intolerance to CPAP. Recent studies show that COMISA is associated with a higher prevalence and incidence of cardiovascular diseases and early mortality compared with OSA alone.^{77,78} This population thus requires highly specialised and personalised care supervised by a sleep specialist. Emerging evidence suggests that cognitive behavioural therapy for insomnia should be proposed prior to starting CPAP as it improves subsequent adherence and patients should remain under the close supervision of a multidisciplinary team.

Minimally symptomatic patients with OSA and unstable cardiovascular comorbidities

In these patients, often only a small improvement in symptoms is seen. This might be linked to poor adherence and high rates of CPAP termination.¹⁴ These patients are also those with the highest risk of high and variable rAHI.⁴⁸ This group requires clinical follow-up with a referent cardiologist and close monitoring of CPAP efficacy data provided by the remote monitoring platform, allow-

Table 1 Gaps or priorities in the domains of research and/or implementation

Problem to address	Potential impact	Proposed solution
Heterogeneity of OSA phenotypes impacting CPAP adherence and risk of CPAP failure	High rate of non-adherence and CPAP termination	Multidimensional data collection for detailed phenotyping and risk prediction of CPAP non-adherence and therapy termination
Allocation of resources to the right patients	Achieve a significant decrease in the societal costs per patient	► Visualisation dashboard for depicting risk allocation ► Simplified follow-up by GPs for low-risk OSA population ► Multidisciplinary care team assisted by remote monitoring platforms for OSA patients at risk of non-adherence and CPAP failure
Share relevant information among caregivers and with patients	Early detection of problems and care adaptation	► CPAP remote monitoring platforms ► PROMs collection using digital tools
Step-by-step analytical approaches and reasoning	Continuous adaptation of care trajectories	► Generation of alerts allowing the implementation of specific interventions
Progression and aggregation of comorbidities	Reduction of OSA-related costs	► Conducting lifestyle interventions in the nutrition and physical activity domains, supported or not by telehealth ► Long-term non-intrusive monitoring of everyday lifestyle behaviours, real-life data on daily activities and physiological parameters via smartphones and wearable devices
Early detection of acute health events essentially related to exacerbations of cardiovascular OSA-related comorbidities (cardiac failure, arrhythmias)	Trigger clinical follow-up with a referent cardiologist and pharmacological adaptation Switch to a more appropriate ventilatory support	► Identify phenotypes at risk of acute events ► Alerts on acute elevation in residual AHI
AHI, Apnoea Hypopnoea Index; CPAP, continuous positive airway pressure; GPs, general practitioners; OSA, obstructive sleep apnoea; PROMs, patient-reported outcome measures.		

ing exacerbations to be anticipated. If necessary, pharmacological treatments may need adjustment and a switch from CPAP to adaptive servo-ventilation should be made.

A dedicated clinic to provide alternative therapies in cases of CPAP termination

In an exhaustive nationwide database of half a million patients, we showed that CPAP termination rates reach 50% at 3 years after CPAP initiation.¹⁴ A large proportion of these patients are subsequently left without treatment. A significant proportion could benefit from alternatives to CPAP13 or the treatment of symptoms, such as wake stimulants for those with persistent daytime sleepiness at risk of traffic accidents.^{79 80} Patients who refuse or abandon CPAP treatment should be managed by tertiary care centres with multidisciplinary expertise able to propose the full spectrum of alternative treatments from mandibular advancement devices to surgery (in particular hypoglossal nerve stimulation and the newly emerging pharmacotherapies).

CONCLUSION AND PERSPECTIVES

There is a pressing need to create new outpatient care pathways to tackle the rising epidemic of OSA and the millions of CPAP-treated patients who need to be followed up. More diversified pathways might provide benefits at both organisational and patient levels. Risk stratification would permit more appropriate patient management, decongesting sleep centres and providing greater equality in access to care. Patients would benefit from earlier intervention, fewer hospital visits, appropriate referral to a variety of specialties covering the full spectrum of sleep disorders and reductions in OSA-related complications and cardiovascular events. A combined digital and in-person model of care would encourage patient engagement and shared decision-making and a better resource allocation between non-physicians and physicians. Table 1 summarises the gaps or priorities in the domains of research and/or implementation. If our field can successfully navigate the implementation and validate the impact of these digital medicine strategies, respiratory sleep medicine could provide a template for other specialties in chronic disease management.⁸

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REFERENCES

- Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7:687–98.
- Lévy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers* 2015;1:15015.
- Mattila T, Hasala H, Kreivi H-R, et al. Changes in the societal burden caused by sleep apnoea in Finland from 1996 to 2018: A national registry study. *Lancet Reg Health Eur* 2022;16:100338.
- Estill J. Knowledge is the key to prevention: Managing the silent epidemic of sleep apnoea. *Lancet Reg Health Eur* 2022;16:100377.
- Cistulli PA, Armitstead J, Pepin J-L, et al. Short-term CPAP adherence in obstructive sleep apnoea: a big data analysis using real world data. *Sleep Med* 2019;59:114–6.
- Sterling KL, Cistulli PA, Linde-Zwirble W, et al. Association between positive airway pressure therapy adherence and health care resource utilization in patients with obstructive sleep apnea and type 2 diabetes in the United States. *J Clin Sleep Med* 2023;19:563–71.
- Wickwire EM, Cole KV, Dexter RB, et al. Depression and comorbid obstructive sleep apnea: Association between positive airway pressure adherence, occurrence of self-harm events, healthcare resource utilization, and costs. *J Affect Disord* 2024;349:254–61.
- Hwang D, Pépin J-L. Sleep Telemedicine: A Template for Other Specialties? *Sleep Med Clin* 2020;15.
- Al-Chalabi S, Alderson H, Garratt N, et al. Improving outpatient clinic experience: the future of chronic kidney disease care and associated multimorbidity. *BMJ Open Qual* 2023;12:e002188.
- Donovan LM, Shah A, Chai-Coetzer CL, et al. Redesigning Care for OSA. *Chest* 2020;157:966–76.
- Marin-Oto M, Vicente EE, Marin JM. Long term management of obstructive sleep apnea and its comorbidities. *Multidiscip Respir Med* 2019;14:21.
- Martinez-Garcia MA, Campos-Rodriguez F, Barbé F, et al. Precision medicine in obstructive sleep apnoea. *Lancet Respir Med* 2019;7:456–64.
- Pépin J-L, Eastwood P, Eckert DJ. Novel avenues to approach non-CPAP therapy and implement comprehensive obstructive sleep apnoea care. *Eur Respir J* 2022;59:2101788.
- Pépin J-L, Baillieu S, Rinder P, et al. CPAP Therapy Termination Rates by OSA Phenotype: A French Nationwide Database Analysis. *J Clin Med* 2021;10:936.
- Pendharkar SR, Tsai WH, Penz ED, et al. A Randomized Controlled Trial of an Alternative Care Provider Clinic for Severe Sleep-disordered Breathing. *Annals ATS* 2019;16:1558–66.
- Pépin J-L, Baillieu S, Tamisier R. Reshaping Sleep Apnea Care: Time for Value-based Strategies. *Ann Am Thorac Soc* 2019;16:1501–3.
- Ryan S, Cummins EP, Farre R, et al. Understanding the pathophysiological mechanisms of cardiometabolic complications in obstructive sleep apnoea: towards personalised treatment approaches. *Eur Respir J* 2020;56:1902295.
- Zinchuk A, Yaggi HK. Phenotypic Subtypes of OSA: A Challenge and Opportunity for Precision Medicine. *Chest* 2020;157:403–20.
- Baillieu S, Destors M, Grillet Y, et al. Obstructive Sleep Apnoea: A Cluster Analysis at Time of Diagnosis. *PLoS One* 2016;11:e0157318.
- Baillieu S, Grote L, Hedner J, et al. Clusters of sleep apnoea phenotypes: A large pan-European study from the European Sleep Apnoea Database (ESADA). *Respirology* 2021;26:378–87.
- Keenan BT, Magalang UJ, Mazzotti DR, et al. Obstructive Sleep Apnea Symptom Subtypes and Cardiovascular Risk: Conflicting Evidence to an Important Question. *Am J Respir Crit Care Med* 2022;205:729–30.
- Gervès-Pingué C, Baillieu S, Goupil F, et al. Positive Airway Pressure Adherence, Mortality, and Cardiovascular Events in Patients with Sleep Apnea. *Am J Respir Crit Care Med* 2022;206:1393–404.

23. Mendelson M, Duval J, Bettega F, et al. The individual and societal prices of non-adherence to continuous positive airway pressure, contributors, and strategies for improvement. *Expert Rev Respir Med* 2023;17:305–17.
24. Carberry JC, Amatoory J, Eckert DJ. Personalized Management Approach for OSA. *Chest* 2018;153:744–55.
25. Bonsignore MR, Suarez Giron MC, Marrone O, et al. Personalised medicine in sleep respiratory disorders: focus on obstructive sleep apnoea diagnosis and treatment. *Eur Respir Rev* 2017;26:170069.
26. McNicholas WT, Korkalainen H. Translation of obstructive sleep apnoea pathophysiology and phenotypes to personalized treatment: a narrative review. *Front Neurol* 2023;14:1239016.
27. Lévy P, Tamisier R, Pépin J-L. Assessment of sleep-disordered-breathing: Quest for a metric or search for meaning? *J Sleep Res* 2020;29:e13143.
28. Soléhac G, Sánchez-de-la-Torre M, Blanchard M, et al. Pulse Wave Amplitude Drops Index: A Biomarker of Cardiovascular Risk in Obstructive Sleep Apnea. *Am J Respir Crit Care Med* 2023;207:1620–32.
29. He S, Cistulli PA, de Chazal P. A Review of Novel Oximetry Parameters for the Prediction of Cardiovascular Disease in Obstructive Sleep Apnoea. *Diagnostics (Basel)* 2023;13:3323.
30. Azarbarzin A, Sands SA, Younes M, et al. The Sleep Apnea-Specific Pulse-Rate Response Predicts Cardiovascular Morbidity and Mortality. *Am J Respir Crit Care Med* 2021;203:1546–55.
31. Trzepizur W, Blanchard M, Ganem T, et al. Sleep Apnea-Specific Hypoxic Burden, Symptom Subtypes, and Risk of Cardiovascular Events and All-Cause Mortality. *Am J Respir Crit Care Med* 2022;205:108–17.
32. Pépin JL, Bailly S, Tamisier R. Incorporating polysomnography into obstructive sleep apnoea phenotyping: moving towards personalised medicine for OSA. *Thorax* 2018;73:409–11.
33. Younes M, Gerardy B, Pack AI, et al. Sleep architecture based on sleep depth and propensity: patterns in different demographics and sleep disorders and association with health outcomes. *Sleep* 2022;45:zsac059.
34. Cistulli PA, Armistead JP, Malhotra A, et al. Relationship between Self-reported Sleepiness and Positive Airway Pressure Treatment Adherence in Obstructive Sleep Apnea. *Ann Am Thorac Soc* 2023;20:1201–9.
35. Chai-Coetzer CL, Antic NA, Rowland LS, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: a randomized trial. *JAMA* 2013;309:997–1004.
36. Antic NA, Buchan C, Esterman A, et al. A randomized controlled trial of nurse-led care for symptomatic moderate-severe obstructive sleep apnea. *Am J Respir Crit Care Med* 2009;179:501–8.
37. Andreu AL, Chiner E, Sancho-Chust JN, et al. Effect of an ambulatory diagnostic and treatment programme in patients with sleep apnoea. *Eur Respir J* 2012;39:305–12.
38. Sánchez-de-la-Torre M, Nadal N, Cortijo A, et al. Role of primary care in the follow-up of patients with obstructive sleep apnoea undergoing CPAP treatment: a randomised controlled trial. *Thorax* 2015;70:346–52.
39. Lloyd R, Morgenthaler TI, Donald R, et al. Quality measures for the care of adult patients with obstructive sleep apnea: 2022 update after measure maintenance. *J Clin Sleep Med* 2022;18:2673–80.
40. Randerath WJ, Herkenrath S, Treml M, et al. Evaluation of a multicomponent grading system for obstructive sleep apnoea: the Baveno classification. *ERJ Open Res* 2021;7.
41. Pépin J-L, Tamisier R, Benjafield AV, et al. CPAP resumption after a first termination and impact on all-cause mortality in France. *Eur Respir J* 2024;63:2301171.
42. Sweetman A, Lack L, Crawford M, et al. Comorbid Insomnia and Sleep Apnea: Assessment and Management Approaches. *Sleep Med Clin* 2022;17:597–617.
43. Bottaz-Bosson G, Hamon A, Pépin J-L, et al. Continuous positive airway pressure adherence trajectories in sleep apnea: Clustering with summed discrete Fréchet and dynamic time warping dissimilarities. *Stat Med* 2021;40:5373–96.
44. Midelet A, Bailly S, Borel J-C, et al. Bayesian Structural Time Series With Synthetic Controls for Evaluating the Impact of Mask Changes in Residual Apnea-Hypopnea Index Telemonitoring Data. *IEEE J Biomed Health Inform* 2022;26:5213–22.
45. Midelet A, Bailly S, Tamisier R, et al. Hidden Markov model segmentation to demarcate trajectories of residual apnoea-hypopnoea index in CPAP-treated sleep apnoea patients to personalize follow-up and prevent treatment failure. *EPMA J* 2021;12:535–44.
46. Redline S, Azarbarzin A, Peker Y. Obstructive sleep apnoea heterogeneity and cardiovascular disease. *Nat Rev Cardiol* 2023;20:560–73.
47. Weaver TE. Best Predictors of Continuous Positive Airway Pressure Adherence. *Sleep Med Clin* 2022;17:587–95.
48. Rossetto A, Midelet A, Baillieu S, et al. Factors Associated With Residual Apnea-Hypopnea Index Variability During CPAP Treatment. *Chest* 2023;163:1258–65.
49. Billings ME, Pendharkar SR. Alternative Care Pathways for Obstructive Sleep Apnea and the Impact on Positive Airway Pressure Adherence. *Sleep Med Clin* 2021;16:61–74.
50. Bughin F, Mendelson M, Jaffuel D, et al. Impact of a telerehabilitation programme combined with continuous positive airway pressure on symptoms and cardiometabolic risk factors in obstructive sleep apnea patients. *D Health* 2023;9.
51. Pépin J-L, Bailly S, Rinder P, et al. Relationship Between CPAP Termination and All-Cause Mortality: A French Nationwide Database Analysis. *Chest* 2022;161:1657–65.
52. Verbraecken J. Telemedicine in Sleep-Disordered Breathing: Expanding the Horizons. *Sleep Med Clin* 2021;16:417–45.
53. Alsaif SS, Kelly JL, Little S, et al. Virtual consultations for patients with obstructive sleep apnoea: a systematic review and meta-analysis. *Eur Respir Rev* 2022;31:220180.
54. Bottaz-Bosson G, Midelet A, Mendelson M, et al. Remote Monitoring of Positive Airway Pressure Data: Challenges, Pitfalls, and Strategies to Consider for Optimal Data Science Applications. *Chest* 2023;163:1279–91.
55. Fox N, Hirsch-Allen AJ, Goodfellow E, et al. The impact of a telemedicine monitoring system on positive airway pressure adherence in patients with obstructive sleep apnea: a randomized controlled trial. *Sleep* 2012;35:477–81.
56. Malhotra A, Crocker ME, Willes L, et al. Patient Engagement Using New Technology to Improve Adherence to Positive Airway Pressure Therapy: A Retrospective Analysis. *Chest* 2018;153:843–50.
57. Hwang D, Chang JW, Benjafield AV, et al. Effect of Telemedicine Education and Telemonitoring on Continuous Positive Airway Pressure Adherence. The Tele-OSA Randomized Trial. *Am J Respir Crit Care Med* 2018;197:117–26.
58. Prigent A, Pellen C, Texereau J, et al. CPAP telemonitoring can track Cheyne-Stokes respiration and detect serious cardiac events: The AlertApnée Study. *Respirology* 2022;27:161–9.
59. Prigent A, Serandour A-L, Luraine R, et al. Interrelated atrial fibrillation and leaks triggering and maintaining central sleep apnoea and periodic breathing in a CPAP-treated patient. *Respirol Case Rep* 2020;8:e00666.
60. Liu D, Armistead J, Benjafield A, et al. Trajectories of Emergent Central Sleep Apnea During CPAP Therapy. *Chest* 2017;152:751–60.
61. Pépin J-L, Woehrle H, Liu D, et al. Adherence to Positive Airway Therapy After Switching From CPAP to ASV: A Big Data Analysis. *J Clin Sleep Med* 2018;14:57–63.
62. Benjafield A, Oldstone L, Willes L, et al. Positive Airway Pressure Therapy Adherence with Mask Resupply: A Propensity-Matched Analysis. *JCM* 2021;10:720.
63. Midelet A, Borel J-C, Tamisier R, et al. Apnea-hypopnea index supplied by CPAP devices: time for standardization? *Sleep Med* 2021;81:120–2.
64. Schmickl CN, Heckman E, Owens RL, et al. The Respiratory Signature: A Novel Concept to Leverage Continuous Positive Airway Pressure Therapy as an Early Warning System for Exacerbations of Common Diseases such as Heart Failure. *J Clin Sleep Med* 2019;15:923–7.
65. Linz D, Baumert M, Desteghe L, et al. Nightly sleep apnea severity in patients with atrial fibrillation: Potential applications of long-term sleep apnea monitoring. *IJC Heart & Vasculture* 2019;24:100424.
66. Howard G, Cushman M, Blair J, et al. Comparative Discrimination of Life's Simple 7 and Life's Essential 8 to Stratify Cardiovascular Risk: Is the Added Complexity Worth It? *Circulation* 2024;149:905–13.
67. McConnell MV, Shcherbina A, Pavlovic A, et al. Feasibility of Obtaining Measures of Lifestyle From a Smartphone App: The MyHeart Counts Cardiovascular Health Study. *JAMA Cardiol* 2017;2:67–76.
68. Sim I. Mobile Devices and Health. *N Engl J Med* 2019;381:956–68.
69. Williams GJ, Al-Baraikan A, Rademakers FE, et al. Wearable technology and the cardiovascular system: the future of patient assessment. *Lancet Dig Health* 2023;5:e467–76.
70. Pépin J-L, Julian-Desayes I, Sapène M, et al. Multimodal Remote Monitoring of High Cardiovascular Risk Patients With OSA Initiating CPAP. *Chest* 2019;155:730–9.
71. Tamisier R, Treptow E, Joyeux-Faure M, et al. Impact of a Multimodal Telemonitoring Intervention on CPAP Adherence in Symptomatic OSA and Low Cardiovascular Risk: A Randomized Controlled Trial. *Chest* 2020;158:2136–45.
72. Murase K, Minami T, Hamada S, et al. Multimodal Telemonitoring for Weight Reduction in Patients With Sleep Apnea: A Randomized Controlled Trial. *Chest* 2022;162:1373–83.
73. Greenhalgh T, Rosen R, Shaw SE, et al. Planning and Evaluating Remote Consultation Services: A New Conceptual Framework Incorporating Complexity and Practical Ethics. *Front Digit Health* 2021;3:726095.
74. Baumert M, Cowie MR, Redline S, et al. Sleep characterization with smart wearable devices: a call for standardization and consensus recommendations. *Sleep* 2022;45:zsac183.
75. Øverby CT, Sutharshan P, Gulbrandsen P, et al. Shared decision making: A novel approach to personalized treatment in obstructive sleep apnea. *Sleep Med X* 2022;4:100052.
76. Sweetman A, Osman A, Lack L, et al. Co-morbid insomnia and sleep apnea (COMISA): recent research and future directions. *Curr Opin Pulm Med* 2023;29:567–73.
77. Lechat B, Appleton S, Melaku YA, et al. Comorbid insomnia and sleep apnoea is associated with all-cause mortality. *Eur Respir J* 2022;60:2101958.
78. Lechat B, Appleton S, Melaku YA, et al. The association of co-morbid insomnia and sleep apnea with prevalent cardiovascular disease and incident cardiovascular events. *J Sleep Res* 2022;31:e13563.
79. Craig S, Pépin J-L, Randerath W, et al. Investigation and management of residual sleepiness in CPAP-treated patients with obstructive sleep apnoea: the European view. *Eur Respir Rev* 2022;31:210230.
80. Steier JS, Bogan RK, Cano-Pumarega IM, et al. Recommendations for clinical management of excessive daytime sleepiness in obstructive sleep apnoea - A Delphi consensus study. *Sleep Med* 2023;112:104–15.

Fibrose pulmonar pode começar na infância: da infância à doença pulmonar intersticial em adultos

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RESUMO

Contexto: A doença pulmonar intersticial na infância (chILD) abrange um grupo de condições respiratórias raras e heterogêneas associadas a significativa morbidade e mortalidade. Relatórios sugerem que muitos doentes diagnosticados com chILD continuam a apresentar uma doença potencialmente progressiva ou fibrótica na idade adulta. Ao longo da última década, o espectro de condições dentro de chILD ampliou-se substancialmente, com a descoberta de novas entidades através de testes genéticos avançados. No entanto, a maioria das evidências está limitada a pequenos estudos de casos, com relatos dispersos em diversas revistas de subespecialidades, clínicas e moleculares. Em particular, a frequência, a gestão e os desfechos da fibrose pulmonar pediátrica não são bem caracterizados, ao contrário dos adultos, para os quais existem diretrizes claras de diagnóstico e tratamento.

Métodos e Resultados: Esta revisão avalia o entendimento atual da fibrose pulmonar em chILD. Com base em dados de registos, foi estimada provisoriamente a ocorrência de fibrose em várias manifestações de chILD, sendo identificadas 47 entidades potencialmente fibróticas de chILD. As evidências publicadas sobre a fibrose no espectro de entidades de chILD foram analisadas, e as questões atuais e futuras na gestão da fibrose pulmonar na infância, com continuidade na idade adulta, foram consideradas.

Conclusões: Há necessidade de melhorar o conhecimento sobre chILD entre pneumologistas para otimizar a transição do cuidado de instalações pediátricas para as de adultos. São necessárias diretrizes atualizadas baseadas em evidências que incorporem recomendações para o diagnóstico e gestão de distúrbios mediados pelo sistema imunitário, bem como de chILD em crianças mais velhas que estão se aproximando da idade adulta.

INTRODUCTION

Childhood interstitial lung disease (chILD) comprises a diverse group of rare respiratory disorders affecting infants, children and adolescents, some of which result in pulmonary fibrosis.^{1–3} Mortality in chILD cohorts may be substantial and estimates have varied in prospective studies between less than 1%⁴ and 30% among infants and 13% overall.⁵ The outcome of individual disease entities is largely unknown, and the exact causes of death often remain unclear. In adults, pulmonary fibrosis is a major cause of death in patients with ILD.⁶ In contrast, in paediatric patients, pulmonary fibrosis is a rare event, with few reports and no systematic prospective studies.⁷ In adults, the definition of fibrosis, early signs of fibrosis and features of progressive pulmonary fibrosis have been extensively investigated, discussed and agreed on in international consensus statements of respiratory societies.^{8–11} In paediatric patients, however, no diagnostic criteria have been established for pulmonary fibrosis and other aspects of fibrotic disease behaviour. Several chILD disorders are genetic in origin, with different defects (and phenotypes) manifesting with increasing age throughout life.¹² While most children with severe lung

developmental conditions such as acinar dysplasia or alveolar capillary dysplasia die in the neonatal period or during infancy,^{13 14} it has become clear that many children with chILD can survive into adulthood, where their disease will fall under the remit of adult physicians and pulmonologists. There is an unmet need for bridging chILD to adult ILD. The goal of this article is to provide state-of-the-art information on fibrosing/potentially fibrosing lung disease in childhood and highlight issues to be addressed in future studies.

DEFINITIONS OF FIBROSIS IN CHILDREN

Fibrosis is defined histopathologically as an increase in collagen deposition and fibroblasts, which may lead to loss of gas-exchange tissue accompanied by lobular remodelling of the parenchyma and microscopic honeycombing (figure 1). The lung can respond to injury with different patterns of interstitial fibrosis, including fibrosing non-specific interstitial pneumonia (NSIP), and, though rare in childhood, usual interstitial pneumonia. The pathology of fibrosing ILD in children overlaps with that in adults, although lobular remodelling with smooth muscle hyperplasia is more prominent in young children (table 1).

While the resolution of CT imaging is much less than that of a lung biopsy, it allows for the assessment of the entire lung parenchyma for findings suggestive of lung disease and fibrosis. Definite signs of fibrosis on CT in children and adults include evidence of traction bronchiectasis and bronchioloectasis (figure 2A) and honeycombing (figure 2B). Architectural distortion is characterised by displacement of pulmonary vessels, airways, fissures and septa (figure 2C and table 1). Areas of reticular opacities, often sub-pleural, are further evidence for fibrosis (figure 2A and table 1). Several of these findings, and especially reticular opacities, can be observed with or without associated ground glass opacities. Importantly, cystic lucencies, particularly when accompanied by ground glass opacities, are an early characteristic of genetically defined surfactant dysfunction disorders (figure 2D), which frequently manifest with fibrosis early in life^{15 16} (see disease-specific sections below). Often the walls of these cysts are barely visible, due to the lack of a thicker fibrous or epithelial wall that often defines cysts.¹⁷ Based on current data, these cystic lesions are included in the imaging criteria for fibrosis. Correlation of these cystic lesions in chILD to the histopathology is needed.

Imaging findings in children need to be correlated with patients' clinical presentation and history and differentiated from lung abnormalities identified on CT scans obtained for other purposes, including staging scans for malignancies, or patients with known cardiac or lung disease not associated with fibrosis. Such findings have been labelled as interstitial lung abnormalities in adults and are present in 33% of undiagnosed first-degree relatives of



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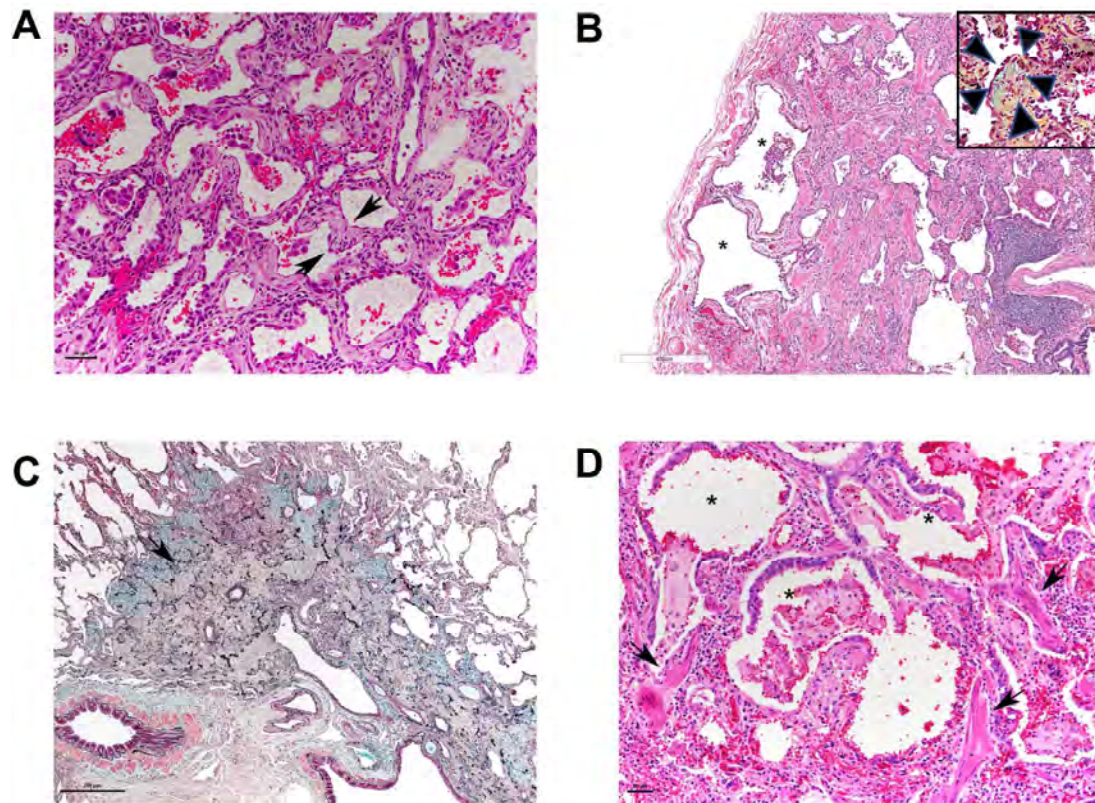


Figure 1 Findings of paediatric pulmonary fibrosis on lung histology. (A) Fibrotic NSIP with uniform expansion of alveolar septa by collagen (arrows) in a 20-month-old with an *SFTPC* mutation (H&E). (B) UIP pattern in an adolescent with an *ABCA3* mutation consists of patchy dense fibrosis accentuated in the subpleural space with honeycomb cystic remodelling (*enlarged, irregular airsaces, H&E) and fibroblastic foci (insert (see arrow heads), Movat stain). (C) Focal dense periairway fibrosis (arrow) is present in a child with restrictive lung disease after bone marrow transplant (Movat stain). (D) Lobular remodelling in a child with *NKX2.1* deficiency is characterised by cystic bronchiolar metaplasia (*) interspersed by bands of smooth muscle (arrows; H&E). *ABCA3*, adenosine triphosphate-binding cassette subfamily A member 3; NSIP, non-specific interstitial pneumonia; *NKX2.1*, *NK2* homeobox 1; *SFTPC*, surfactant protein C; UIP, usual interstitial pneumonia.

patients with IPF,¹⁸ although they have not yet been investigated in children.

Understanding that lungs are constantly developing in children and that the postnatal lung has an enormous repair potential into adolescence is of pivotal importance when considering the genesis of fibrosis in childhood. How fibrosis evolves in the developing lung, and during the disease course of various conditions, and if all aspects are irreversible, is largely unexplored and requires investigation.

DEFINITION OF PROGRESSIVE FIBROSIS IN CHILDREN

In adults, progressive pulmonary fibrosis is defined in clinical practice guidelines by worsening of any two of the following three parameters over 12 months with no alternative explanation: respiratory symptoms, lung function (absolute decline in forced vital capacity $\geq 5\%$ or absolute decline in diffusing capacity of the lung for carbon monoxide (DLCO) $\geq 10\%$) or radiological changes.¹⁰ ‘Radiological changes’ encompass increased extent or severity of traction bronchiolectasis and bronchiectasis, new associated ground-glass opacity, new fine reticulation, increased extent or coarseness of reticulation, new or increased honeycombing and increased volume loss.¹⁰ Longitudinal data in children are scarce, but cystic lesions increase over time in number and size in

both surfactant protein C (SP-C) deficiency¹⁵ and adenosine triphosphate-binding cassette subfamily A member 3 (*ABCA3*) deficiency,¹⁶ again supporting their role in paediatric lung fibrosis.

ILD disease trajectory may differ between adults and children of different age groups² with possible differences in histological and radiological findings between children and adults. Changes in lung function in children occurring in the context of ongoing postnatal lung development further complicate the identification of progressive fibrosis in children.⁷ In addition, in children, valid lung function measurements are usually not available until the age of 6 years and DLCO measurement is not available until the vital capacity is at least 1000 mL. Thus, detection of disease progression in young children with chILD is difficult, and not possible using adult criteria.

CHILD NATURAL DISEASE COURSE AND PULMONARY FIBROSIS

In the last decade, the increased availability of genetic testing has led to the discovery of many genetic defects associated with novel entities of chILD, with different phenotypes and pathologies manifesting with increasing age.¹² However, the natural history of most chILD entities is not yet determined. Whereas some remit and never become symptomatic in adults,^{19–20} chILD disorders may also have sustained chronic parenchymal inflammation and progress to fibrosis.^{21,22} In adults, data on the exact or estimated proportion of patients with progressive fibrosis among the various types of ILD are limited²³ while in children no such data are available. As an initial approach we searched the European- and US-chILD registries for the presence or absence of cases with diagnosed fibrosis.

FIBROSIS IN DIFFERENT CHILD ENTITIES

Analysis of the chILD-EU and US-chILD registries identified 47 distinct entities where fibrosis has been recorded (box 1).

Important entities manifesting fibrosis are discussed below. Figure 3 shows lung histology in some of these entities while CT patterns are shown in figure 4.

Table 1 Criteria for the definition of fibrosing ILD

Evidence of fibrosing ILD	
Lung biopsy	HRCT scan
▶ Evidence of interstitial fibrosis ▶ Evidence of lobular remodelling ▶ Honeycombing ▶ NSIP (fibrosing) ▶ UIP	▶ Traction bronchiectasis ▶ Architectural distortion ▶ Honeycombing ▶ Reticular abnormality ▶ Cystic abnormalities*
*Not commonly accepted as a criterion for fibrosis in adult ILD	

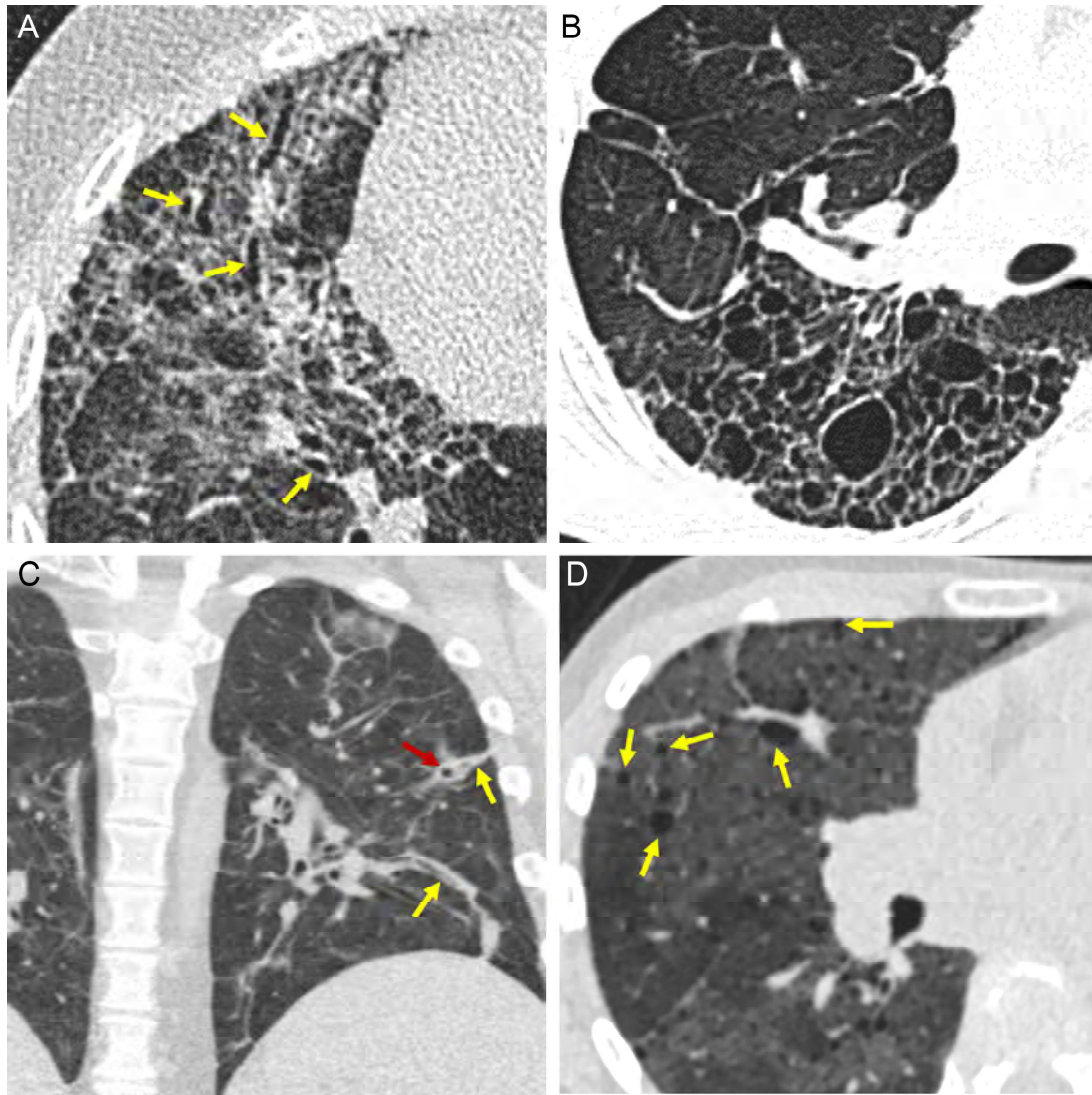


Figure 2 Findings of paediatric pulmonary fibrosis on chest CT. (A) Reticular opacity consisting of mesh/net-like opacities associated with traction bronchiectasis with irregular bronchiolar dilation (yellow arrows) in an 11-year-old with a history of ARDS. (B) Honeycombing consisting of clustered enlarged airspaces with defined walls in a 15-year-old male with chILD of unknown aetiology. (C) Architectural distortion with deformation of the fissures, parenchymal bands consisting of irregular linear opacities, some of which extend to the pleural surface (yellow arrows) and traction bronchiectasis (red arrow) in a 19-year-old female with post-COVID-19 fibrosis. (D) Cystic lucencies with rounded areas of decreased density without defined wall (yellow arrows) in a 10-year-old patient with an *ABCA3* mutation. *ABCA3*, adenosine triphosphate-binding cassette subfamily A member 3; ARDS, acute respiratory distress syndrome; chILD, childhood interstitial lung disease.

LUNG-NATIVE PARENCHYMAL DISORDERS

Surfactant dysfunction disorders caused by pathogenic variations in the genes for *ABCA3* (*ABCA3*) and *SP-C* (*SFTPC*) can manifest in childhood with consequences in later life.^{15 24}

ABCA3 deficiency

ABCA3 is an intracellular transmembrane glycoprotein that facilitates the packaging and transport of surfactant into lamellar bodies of type 2 pneumocytes.²⁵ More than 200 *ABCA3* variants leading to loss of function have been described and are implicated in inherited pulmonary diseases with varying phenotypes, from potentially fatal neonatal respiratory distress syndrome to diffuse parenchymal lung diseases in childhood or even adulthood.^{16 24 26} Progression to fibrosis is frequently reported in patients with *ABCA3* mutations and ILD, generally increasing with age.^{16 24 27} Figures 1B, 2D show lung histological and chest CT characteristics of children with *ABCA3* deficiency.

SP-C dysfunction disorder

SP-C dysfunction disorder is an inherited autosomal dominant disease caused by a mutation in the *SFTPC* gene.^{15 28 29} A former study categorised 17 patients who had a heterozygous dominant mutation in the *SFTPC* gene according to their typical characteristics and age.¹⁵ Three categories of presentation were defined as (1) neonatal respira-

tory distress syndrome, as originally described for surfactant protein B deficiency,³⁰ often with a family history of lung disease, previous pregnancy, miscarriage or postnatal death; (2) the classical presentation of infants with tachypnoea, dyspnoea and failure to thrive, diffuse ground glass opacity on chest CT within the first few months, with pathological findings of NSIP, or a combination of pulmonary alveolar proteinosis (PAP), NSIP and desquamative interstitial pneumonia and (3) late childhood, adolescence or adulthood diagnosis of chronic pulmonary fibrosis^{15 31} with progressive findings of increased cystic lucencies and reticular opacities on chest CT.³² Figures 1A, 4A show lung histological and chest CT characteristics of children with an *SFTPC* mutation.

SYSTEMIC DISEASE-RELATED DISORDERS

Children often present with pulmonary manifestations of systemic diseases, which can be associated with high morbidity and mortality. In a subset of patients, pulmonary disease may be the predominant initial clinical presentation. It is, therefore, important for paediatric pulmonologists to consider systemic diseases when making a diagnosis.³³

Systemic disease-related disorders in immunocompetent children Conditions with a predominant lung phenotype

Causes of chILD that have been linked with pulmonary fibrosis include mutations affecting fibroblast growth factor 10 (*FGF10*) and

Box 1 Conditions in the chILD-EU and US-chILD registries where pulmonary fibrosis has been described, ordered according to their disease categories (lung-native disorders (native diffuse parenchymal disorders), systemic disease-related disorders and exposure-related disorders).

Lung-native disorders (lung only)

Surfactant protein C mutations

ABCA3 deficiency

Non-specific interstitial pneumonia
Combined pulmonary fibrosis and emphysema
Bronchopulmonary dysplasia
Bronchiolitis obliterans
Surfactant protein B mutations
Wilson Mikity, new bronchopulmonary dysplasia

Systemic disease-related disorders

STING-associated vasculopathy (SAVI)

Hermansky-Pudlak Type 2

FARS1 associated disease

Juvenile systemic sclerosis

Mixed connective tissue disease
Undifferentiated connective tissue disease
Collagen vascular disorders
GATA2

Systemic juvenile arthritis-associated lung disease
Sarcoidosis

Bone marrow transplantation

Bronchiolitis obliterans after bone marrow transplantation

RAB5B deficiency

COPA defect

Systemic lupus erythematosus

STAT3 GOF mutation

TBX4 mutation

NKX2.1 gene defect

MARS-associated disease

Telomerase complex mutations

Integrin $\alpha 3$ -disease

MDA-5 JDM

Hereditary PAP

Rubinstein-Taybi syndrome

FINCA syndrome

Juvenile myelomonocytic leukaemia

Antisynthetase syndrome

IgG4-related disease

Ectodermal dysplasia

Ataxia telangiectasia

Related to trisomy 21

Filamin A mutation

FGF10

Granulomatosis with polyangitis

Exposure-related disorders

Radiation lung injury

Hypersensitivity pneumonitis

Drug reactions

Toxic inhalation

Aspiration syndromes

ABCA3, adenosine triphosphate-binding cassette subfamily A member 3; chILD, childhood interstitial lung disease; COPA, coatomer protein

Continued

Box 1 Continued

subunit alpha; FARS1, phenylalanine-tRNA synthetase 1; FINCA, fibrosis, neurodegeneration and cerebral angiomas; GATA2, GATA binding protein 2; MARS, methionyl-tRNA synthetase; NKX2.1, NK2 homeobox 1; PAP, pulmonary alveolar proteinosis; RAB5B, Ras-related protein Rab-5B; STAT3-GOF, signal transducer and activator of transcription 3 gain of function; STING, stimulator of interferon genes; TBX4, T-box transcription factor 4.

Conditions discussed further below are in bold.

its receptor FGFR2,³⁴ brain–thyroid–lung syndrome/NKX2.1 deficiency,³⁵ T-box transcription factor 4 (TBX4) syndrome,³⁶ filamin A (FLNA) deficiency^{37,38} and RAB5 deficiency.³⁹ Due to the rarity of these diseases, their frequency and the extent of fibrosis are largely unknown.

MARS1 deficiency

A severe form of childhood PAP caused by biallelic missense mutations in the methionyl-tRNA synthetase 1 gene (MARS1) has been reported, with high prevalence localised to the island of La Réunion in the Western Indian Ocean.⁴⁰ MARS1 encodes for cytosolic MARS1 and plays a pivotal role in protein biosynthesis. Patients present with respiratory insufficiency, PAP, progressive pulmonary fibrosis (in about 50% by the age of 14 years), and structural hepatopathy, with high rates of mortality reported.⁴¹ A recent study of two cases with pathogenic biallelic MARS1 gene mutations demonstrated a multisystemic phenotype not restricted to the lung and liver, treatable with a methionine-rich diet.⁴⁰ CT findings in patients with MARS1 deficiency have included ground glass opacities with septal thickening resulting in a crazy paving pattern.^{40,42}

FARS1-related disorders

Three comparative MRMC studies reported on the impact of AI assistance on reading times.^{18,22,23} Reading times were significantly faster with AI assistance compared with unaided readers: median 86 (IQR 51–141) seconds vs 160 (IQR 96–245) seconds ($p<0.001$)²² and mean 98.0 seconds vs 132.3 seconds per case ($p<0.01$)¹⁸ for radiologists, and median 3 (IQR 2–5) and 5 (IQR 4–8) min for radiographers using AI in a laboratory (ie, non-clinical) setting vs 10 (IQR 5–15) min for radiologists (unassisted reading in clinical practice).²³

Fibrosis, neurodegeneration and cerebral angiomas syndrome

Rare biallelic missense variants in NHL repeat containing protein 2 (NHLRC2) have recently been discovered to cause fibrosis, neurodegeneration and cerebral angiomas (FINCA) syndrome, a combination of pulmonary fibrosis, neurodegeneration and cerebral angiomas.⁴⁷ The associated phenotype can be lethal in infancy, and a small number of cases have reported initial presentation of ILD combined with neurodevelopmental delay and multiorgan involvement.^{47,48} Recently, a study using the chILD-EU register database found that some patients experience stabilisation of their lung disease over time and survive into childhood, suggesting that FINCA syndrome should be considered at all ages, including in patients with a history of stabilising chILD who have neurodevelopmental delay.⁴⁹ Chest CT findings were variable including ground glass opacities, consolidation, cysts and overinflation. Of interest, NHLRC2 expression is increased in idiopathic pulmonary fibrosis in adults.⁵⁰

Systemic disease-related disorders with features of immunodeficiency/immunodysregulation/autoinflammation Rheumatological disorders

Pulmonary disease is more common in certain autoimmune rheumatological diseases typically diagnosed after 6 years of age and driven by the adaptive immune system (ANCA-associated vasculitis, Ribonucleoprotein (RNP)-associated systemic lupus erythematosus (SLE), melanoma differentiation-associated protein 5 (MDA-5) juvenile dermatomyositis (JDM), juvenile systemic sclerosis (JSSc).

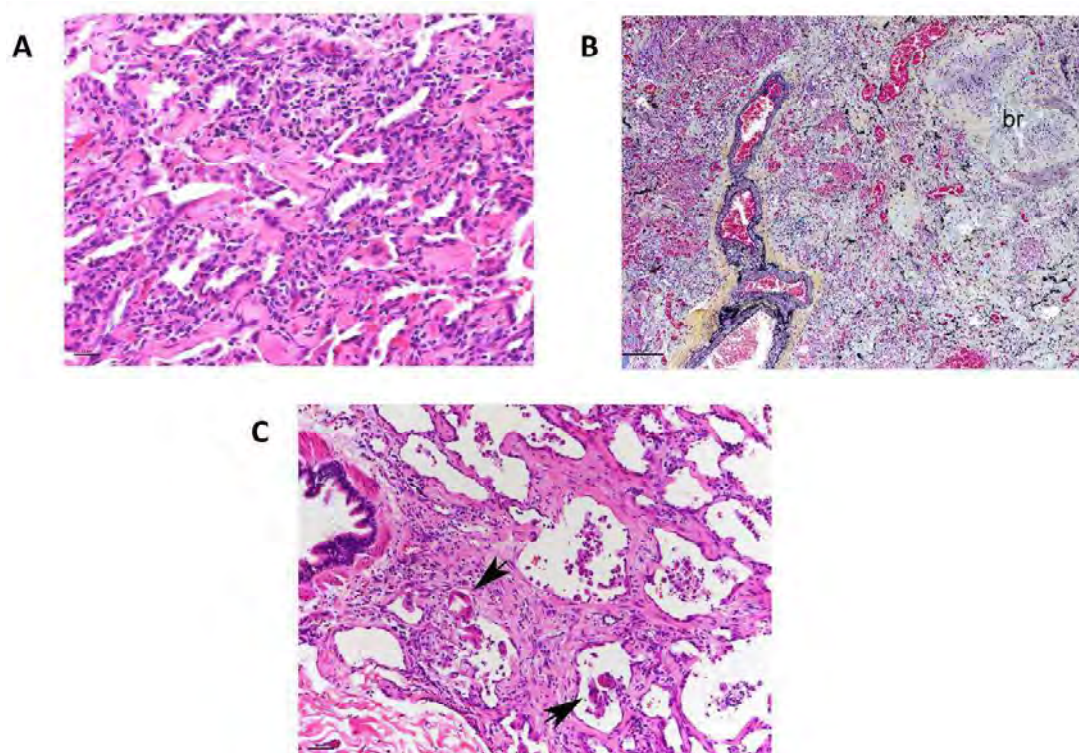


Figure 3 Lung histology findings of children with specific chILD entities. (A) Cellular and fibrotic NSIP seen in an adolescent later diagnosed with polymyositis (H&E). (B) Child with SAVI has dense interstitial fibrosis and occlusive airway fibrosis (Movat stain). (C) Peribronchiolar fibrosis with isolated multinucleated giant cells (arrows) in a child with hypersensitivity pneumonitis (H&E). chILD, childhood interstitial lung disease; NSIP, non-specific interstitial pneumonia; SAVI, stimulator of interferon genes-associated vasculopathy of infancy.

ANCA-associated vasculitis

In paediatric ANCA-associated vasculitis (pAAV), pulmonary involvement is very common, with higher prevalence in eosinophilic granulomatosis with polyangiitis (EGPA (88%)) compared with GPA (52%–74%) and microscopic polyangiitis (MPA (29%–44%)) although EGPA is much less common⁵¹; often pAAV presents with periods of high acuity with overt respiratory symptoms such as chronic cough, exertional dyspnoea, haemoptysis and respiratory distress secondary to haemorrhage and vasculitis, especially in GPA compared with MPA and unclassified AAV. However, paediatric patients can also be asymptomatic with their lung disease evolving into fibrotic interstitial changes,⁵² especially in MPA. Imaging findings of AAV include ground glass opacities and areas of consolidation as well as centrilobular and larger nodules, characteristic of pulmonary haemorrhage.⁵³

Systemic lupus erythematosus

SLE has a high prevalence of pulmonary disease (up to 40% within the first year)⁵⁴; a common acute presentation with a good prognosis is pleuritis; less common acute presentations involve acute lupus pneumonitis (ALP; <10%) of which about 3% may lead to chronic ILD.⁵⁵ The increased risk factors for ILD (eg, anti-RNP, ANCA, severe SLE activity) remain controversial. Common findings on CT in patients with SLE include ground glass opacities, septal thickening and diffuse consolidation, each of which are seen in more than 50% of patients. Other common findings include patchy consolidations, fibrotic changes and pleural effusions.⁵⁶ Other chronic presentations include shrinking lung disease (<1%) and pulmonary hypertension (5%–14%).

Melanoma differentiation-associated protein 5 juvenile dermatomyositis

MDA-5 associated JDM (<5% of total JDM subtypes in the USA and UK) has a high prevalence of rapidly progressive ILD leading to alveolar fibrosis.⁵⁷ In a Japanese study, 31% of patients with MDA-5 JDM developed ILD, which was rapidly progressing in 50% of cases.⁵⁸ Radiological patterns in MDA-5 JDM are often described when the

patient is symptomatic with a rapidly evolving course with ground glass opacities and multifocal areas of consolidation, sometimes complicated by pneumothorax and pneumomediastinum. In some cases, this may progress quickly to findings of fibrosis including reticular opacities, traction bronchiectasis and architectural distortion.⁵⁹

Juvenile systemic sclerosis

jSSc is an autoimmune disease with an indolent subclinical pulmonary course that can be detected early. Although jSSc is rare, pulmonary disease ranges from 35% to 55% and includes ILD, pulmonary arterial hypertension secondary to ILD and vasculopathy.⁶⁰ Early chest CT findings typically reflect alveolitis, with ground glass opacities and micronodules that progress slowly to fibrosis with findings of reticular opacities, traction bronchiectasis, honeycombing, cystic changes and architectural distortion.⁶¹ Despite these findings, many patients with jSSc can be asymptomatic, especially early in the disease course.

Autoinflammatory diseases

Unlike autoimmune rheumatological disease, autoinflammatory diseases develop earlier in childhood and are driven more by the innate immune system. These include COPA (coatamer protein complex subunit alpha) (syndrome) and stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI).

Coatamer protein complex subunit alpha

COPA is a monogenic endoplasmic reticulum stress disease leading to lung inflammation and scarring typically presenting (76%) before age of 5 years⁶²; pulmonary manifestations (chronic cough, tachypnoea, dyspnoea) are common due to capillaritis and alveolar haemorrhage or ILD associated with lymphoid hyperplasia and follicular bronchiolitis, lymphocytic interstitial pneumonia (LIP), pulmonary cysts and fibrosis; a unique CT pattern is diffuse ground glass opacity, septal thickening and cysts and centrilobular nodules. Common chest CT findings such as ground glass opacities and pulmonary nodules, can improve while cysts, septal thickening and fibrosis may

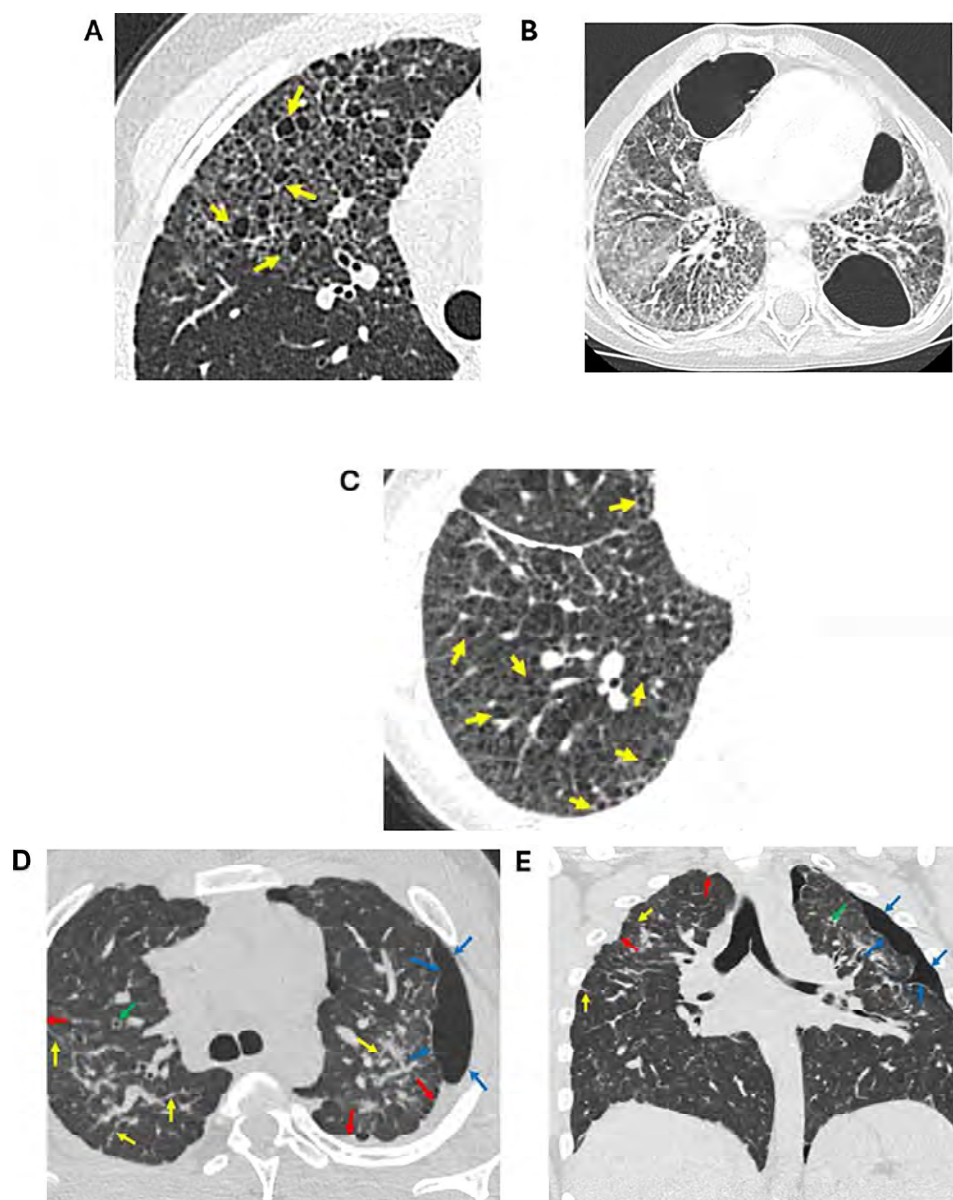


Figure 4 CT patterns of children with specific chILD entities. (A) *SFTPC* mutation in a 6-year-old with reticular opacities and cystic lucencies (yellow arrows) on axial CT image. (B) SAVI in a patient aged 7 years, with diffuse ground glass and reticular opacities with large cystic lesions on axial CT image. (C) COPA syndrome in a 13-year-old with diffuse reticular opacities and cystic lucencies (yellow arrows). (D, E) PPFE in a 15-year-old with papillary thyroid cancer with pleural thickening (red arrows), septal thickening, yellow arrows, traction bronchiectasis (green arrows) and pneumothorax (blue arrows) on (D) axial and (E) coronal images. COPA, coatomer protein subunit alpha; SAVI, stimulator of interferon genes-associated vasculopathy of infancy, *SFTPC*, surfactant protein C gene.

progress (figure 4C).⁶³ As COPA has variable clinical penetrance, patients can be asymptomatic but universally develop progressive lung disease with worsening pulmonary function due to pulmonary haemorrhage, which can be insidious, or ILD.

STING-associated vasculopathy with onset in infancy

SAVI is a monogenic, autosomal dominant type I interferonopathy caused by gain-of-function variants in transmembrane protein 173 (TMEM173), which presents typically early in life with cough, tachypnoea, exertional dyspnoea, haemoptysis in association with ILD (75%). Chest CT imaging demonstrates ground glass opacities, septal thickening, reticular opacities and cysts that can be seen in lung fibrosis.⁶⁴ However, the severity and natural course of lung disease vary even within the same mutation.⁶⁵ Figures 3B, 4B show lung histological and chest CT characteristics of children with SAVI.

Hermansky-Pudlak syndrome

Hermansky-Pudlak syndrome (HPS) is a rare hereditary disorder of albinism and bleeding diathesis.⁶⁶ There are at least 11 different

forms of HPS caused by mutations in different genes.^{66–67} While all have oculocutaneous albinism and bleeding diathesis due to platelet dysfunction, other organ manifestations are variable. For HPS1 and HPS4, pulmonary fibrosis has been reported in early adulthood but typically occurs in middle-aged adults,^{68,69} whereas children with HPS2 may develop ILD and pulmonary fibrosis.⁶⁶ In the lungs, dysfunctional type 2 epithelial cells interact with macrophages, other immune cells and fibroblasts to generate fibrotic remodelling of the tissue.^{66–70–71} CT findings in patients with HPS include ground glass opacities, reticulation and traction bronchiectasis.

STAT3-GOF variants

Signal transducer and activator of transcription 3 gain-of-function (STAT3-GOF) variants cause severe multisystem autoimmunity, with ILD manifestations developing in approximately one-third of patients. A recent case study identified two new lung-predominant STAT3 variants, which manifested as severe ILD during the first 3 years, highlighting the importance of closely monitoring pulmonary function in patients known to carry STAT3-GOF alleles.⁷² Other

disorders associated with immune-dysregulated ILD in children include LIP and granulomatous lymphocytic ILD.

Telomeropathies

While mutations in genes of the telomere complex can play a major role in fibrosis in adults,³¹ this is relatively rare in paediatric patients but may cause fibrosis.⁷³ In children with variants of the dyskeratosis congenita gene, DKC1, lung fibrosis can also be observed (Hoyeraal-Hreidarsson syndrome).⁷⁴

EXPOSURE-RELATED DISORDERS

Exogenous allergic alveolitis/hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is a group of immunologically mediated lung diseases caused by an immunoglobulin G-mediated hypersensitivity reaction to an environmental trigger. This leads to inflammation of the distal bronchioles and alveoli, often with granulomas and, if not diagnosed and treated, may lead to chronic severe lung disease including progressive fibrosis, emphysema and secondary pulmonary hypertension.⁷⁵ Figure 3C shows lung histological fibrosis characteristics of a child with HP. CT findings of HP include ground glass opacities, centrilobular nodules and mosaic attenuation in the acute and subacute phases and can progress to include fibrotic changes such as reticulation, traction bronchiectasis and honeycombing in chronic HP.

Pulmonary fibrosis or pleuroparenchymal fibroelastosis following radiation, chemotherapy or stem cell transplant

It has long been recognised that allogeneic bone marrow transplantation in children is associated with fibrotic pulmonary complications.⁷⁶ In the last decade, there have been developments in our understanding of ILD entities following autologous stem cell transplant, including non-infectious idiopathic pneumonia syndrome (IPS).⁷⁷ More recently, in a study of 340 paediatric patients treated with high-dose chemotherapy and autologous haematopoietic stem cell transplantation (HSCT), 2.4% developed non-infectious ILD.⁷⁸ Lung biopsies showed interstitial fibrosis and/or septal expansion from inflammatory cells and pleural thickening.⁷⁸

Pleuroparenchymal fibroelastosis (PPFE) represents fibrosis of the pleura and subpleural parenchyma, dominating the upper lung lobes. On CT, patients present with areas of pleural thickening, traction bronchiectasis, architectural distortion and consecutive volume loss (figures 4D, E). Many patients may have a flattened chest (platythorax). Pneumothorax is a common complication. Histology shows fibrosis with a particular abundance of elastic fibres. In contrast to adults, in children only one case of idiopathic PPFE has been reported,⁷⁹ with secondary PPFE more frequent, having an incidence of 4% after HSCT and previous chemotherapy or radiotherapy.⁸⁰ Following SCT, the median overall survival with PPFE was only 6.8 years.⁸⁰ Whereas the combined presence of bronchiolitis obliterans, organising pneumonia and IPS increased the risk of PPFE by about 2.5-fold, pneumonia more than 3 months after SCT increased the risk by about 10-fold. In lung transplanted subjects, PPFE may be a manifestation of chronic lung rejection.⁸¹

TREATMENT OF FIBROSING CHILD

Pulmonary fibrosis is a consistent response pattern of the lungs to a variety of injuries. As indicated above, these include endogenous factors like autoinflammatory, autoimmune and strong genetic drivers, and noxious exogenous factors. Second hits, such as acute exacerbations due to respiratory tract infections, have been shown to have a significant and deleterious effect on the clinical course of and health-related quality of life in chILD.⁸² Thus, management targeting these underlying factors is likely to ameliorate the driving forces towards inflammation and fibrosis.⁷

All recommendations are limited by the absence of appropriate randomised controlled clinical trials. Besides supportive treatments in the form of oxygen supplementation and/or ventilation, adequate caloric intake, psychosocial support and physiotherapeutic rehabilitation, clinical management is currently guided by indirect evidence, case reports and clinical experience.^{183–86} Prophylactic

immunisations may reduce the risk of exacerbations.⁸⁷ Patients with autoimmune disorders may be treated with steroids¹ and potentially steroid-sparing immunosuppressive medications such as mycophenolate mofetil (MMF), azathioprine, intravenous immunoglobulin, cyclophosphamide and calcineurin inhibitors.⁸⁸ Inhibitors of Janus kinase such as baricitinib and ruxolitinib may also be an effective treatment of autoinflammatory interferonopathies, such as SAVI, STAT3-GOF and COPA, and several case studies have demonstrated promising results.^{89–91} In addition, biologics such as rituximab, an anti-CD20 monoclonal antibody, have shown promising effects in treating immune-mediated diseases, with several studies showing efficacy in treating systemic sclerosis in adults and children, including one study combining rituximab with MMF.^{92–95}

The anti-inflammatory agents hydroxychloroquine and azithromycin have been included in treatment protocols for chILD.¹ The first randomised, placebo-controlled trial in chILD, which included a large fraction of potentially fibrosing chILD with a mean forced vital capacity of approximately 50% of predicted, was a recently completed phase II study of hydroxychloroquine in 29 children.⁹⁶ Although the study failed to document treatment efficacy, partly because of its small size, hydroxychloroquine was well tolerated. While larger studies will be necessary, the results suggest that the previous optimistic appraisal of hydroxychloroquine use in chILD should be evaluated further.

The InPedILD trial, a double-blind, randomised, placebo-controlled clinical trial of nintedanib in children and adolescents (6–17 years) with clinically significant fibrosing chILD, used a definition of paediatric lung fibrosis based on the imaging and histology criteria to identify eligible patients for enrolment.⁹⁷ Fibrosis was diagnosed by the presence of one of the biopsy criteria and one or more high-resolution CT (HRCT) findings, excluding cystic abnormalities, ≤ 12 months before screening or, in the absence of a biopsy with fibrosis, by the presence of two or more HRCT findings, including cystic abnormalities on ≥ 2 scans, with the most recent performed ≤ 12 months before screening. The safety and tolerability profile of nintedanib therapy was favourable in children with established fibrosis aged ≥ 6 years included in InPedILD.^{97–98} Exploratory analyses of efficacy showed encouraging activity. Although the difference was not significant, patients in the nintedanib group had a mean increase in forced vital capacity of $0.3\% \pm 1.3\%$ predicted at 24 weeks compared with a decline of $0.9\% \pm 1.8\%$ in the placebo group (nominal $p=0.60$).⁹⁷ Bayesian analysis indicated a median difference of 1.63% (95% credible interval -0.69 to 3.40).⁹⁸

FUTURE DIRECTIONS

Clinical and translational investigations into condition-specific development of pulmonary fibrosis in infants and children are needed to define the mostly unknown natural disease course as well as the disease mechanisms in which injury, repair and fibrosis occur in the context of normal lung growth. Transfer of advances already achieved from the intense study of idiopathic pulmonary fibrosis in adults into childhood may speed up the introduction of successful treatments in younger patients.

The definition of fibrosis detailed here and used in InPedILD needs to be further substantiated and may provide a model for future placebo-controlled randomised trials that assess whether the development or progression of pulmonary fibrosis can be prevented. For drug trials in adults that are supported by pharmaceutical companies, investigational plans should be extended to the paediatric age groups, if possible. Similarly, investigator-initiated studies in adults should be re-evaluated for the inclusion of paediatric centres with appropriate expertise.

An exploitable advantage of many of the chILD conditions is knowledge about their molecular basis and disease pathways, which may be targeted by personalised therapy. For example, high-content screening of US Food and Drug Administration-approved small molecules identified ciclosporin A as a potent corrector of some ABCA3 mutation variants.⁹⁹ Repurposing of approved drugs may help to facilitate treatment options for some conditions including ABCA3 deficiency. Gene therapy is a promising option to treat lung

diseases due to monogenetic causes like SP-B-, SP-C and ABCA3 deficiency.¹⁰⁰ Use of induced pluripotent stem cell (iPSC) technology (eg. iPSC systems carrying the ILD-associated SFTPC variant) can also be helpful for disease modelling and assessment of novel therapeutics.¹⁰¹

CONCLUSIONS

In the last decade, there have been developments in our understanding of the genetic component of chILD and the progression of certain disorders into adulthood. With the discovery of novel entities, there is a need for improved knowledge of chILD among pulmonologists to optimise the transition of care from paediatric to adult facilities. Updated evidence-based guidelines are needed that incorporate recommendations for the diagnosis and management of immune-mediated disorders, as well as chILD in older children approaching adulthood. Translational and clinical research into the mechanisms of fibrosing pathways in well-defined chILD is critical to develop targeted strategies. Monitoring disease progression and developing a therapeutic strategy to prevent pulmonary fibrosis or its progression are imperative for the future treatment of ILD in children and adolescents, and when they move into adult care.

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REFERENCES

- Bush A, Cunningham S, de Blic J, et al. European protocols for the diagnosis and initial treatment of interstitial lung disease in children. *Thorax* 2015;70:1078–84.
- Fan LL, Dishoff MK, Galambos C, et al. Diffuse lung disease in biopsied children 2 to 18 years of age. Application of the chILD classification Scheme. *Ann Am Thorac Soc* 2015;12:1498–505.
- Detering RR. Children's interstitial and diffuse lung disease: Progress and future horizons. *Ann Am Thorac Soc* 2015;12:1451–7.

- Torrent-Vernetta A, Gaboli M, Castillo-Corullón S, et al. Incidence and prevalence of children's diffuse lung disease in Spain. *Arch Bronconeumol* 2022;58:22–9.
- Griese M, Haug M, Brasch F, et al. Incidence and classification of pediatric diffuse parenchymal lung diseases in Germany. *Orphanet J Rare Dis* 2009;4:26.
- Cottin V, Teague R, Nicholson L, et al. The burden of progressive-fibrosing interstitial lung diseases. *Front Med (Lausanne)* 2022;9:799912.
- Nathan N, Sileo C, Thouvenin G, et al. Pulmonary fibrosis in children. *J Clin Med* 2019;8.
- Travis WD, Costabel U, Hansell DM, et al. An official american thoracic society/ european respiratory society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013;188:733–48.
- Hatabu H, Hunninghake GM, Richeldi L, et al. Interstitial lung abnormalities detected incidentally on CT: a position paper from the Fleischner society. *Lancet Respir Med* 2020;8:726–37.
- Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ats/ers/jrs/alat clinical practice guideline. *Am J Respir Crit Care Med* 2022;205:e18–47.
- Rahaghi FF, Hsu VM, Kaner RJ, et al. Expert consensus on the management of systemic sclerosis-associated interstitial lung disease. *Respir Res* 2023;24:6.
- Griese M. Etiologic classification of diffuse parenchymal (interstitial) lung diseases. *J Clin Med* 2022;11:1747.
- Oneto S, Poppitt RJ. Congenital acinar dysplasia: a lethal entity. *Autops Case Rep* 2019;9:e2019119.
- Bishop NB, Stankiewicz P, Steinhorn RH. Alveolar capillary dysplasia. *Am J Respir Crit Care Med* 2011;184:172–9.
- Kröner C, Reu S, Teusch V, et al. Genotype alone does not predict the clinical course of SFTPC deficiency in paediatric patients. *Eur Respir J* 2015;46:197–206.
- Kröner C, Wittmann T, Reu S, et al. Lung disease caused by ABCA3 mutations. *Thorax* 2017;72:213–20.
- Hansell DM, Bankier AA, MacMahon H, et al. Fleischner society: glossary of terms for thoracic imaging. *Radiology* 2008;246:697–722.
- Hunninghake GM, Quesada-Arias LD, Carmichael NE, et al. Interstitial lung disease in relatives of patients with pulmonary fibrosis. *Am J Respir Crit Care Med* 2020;201:1240–8.
- Rauch D, Wetzel M, Reu S, et al. Persistent tachypnea of infancy: Usual and aberrant. *Am J Respir Crit Care Med* 2016;193:438–47.
- Seidl E, Carlsen J, Reu S, et al. Pulmonary interstitial glycogenosis – a systematic analysis of new cases. *Respir Med* 2018;140:11–20.
- Clement A, Force ERST. Task force on chronic interstitial lung disease in immunocompetent children. *Eur Respir J* 2004;24:686–97.
- Hartl D, Griese M. Interstitial lung disease in children -- genetic background and associated phenotypes. *Respir Res* 2005;6:32.
- Olson AL, Patnaik P, Hartmann N, et al. Prevalence and incidence of chronic fibrosing interstitial lung diseases with a progressive phenotype in the united states estimated in a large claims database analysis. *Adv Ther* 2021;38:4100–14.
- Manali ED, Legendre M, Nathan N, et al. Bi-allelic missense abca3 mutations in a patient with childhood ILD who reached adulthood. *ERJ Open Res* 2019;5:2019.
- Wittmann T, Schindlbeck U, Höppner S, et al. Tools to explore ABCA3 mutations causing interstitial lung disease. *Pediatr Pulmonol* 2016;51:1284–94.
- Wittmann T, Frixel S, Höppner S, et al. Increased risk of interstitial lung disease in children with a single R288K variant of ABCA3. *Mol Med* 2016;22:183–91.
- Li Y, Seidl E, Knoflach K, et al. Surviving ABCA3-related interstitial lung disease beyond infancy. *Thorax* 2023;78:587–95.
- Willander H, Askari G, Landreh M, et al. High-resolution structure of a BRICHOS domain and its implications for anti-amyloid chaperone activity on lung surfactant protein C. *Proc Natl Acad Sci U S A* 2012;109:2325–9.
- Nogee LM, Dunbar AE, Wert SE, et al. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. *N Engl J Med* 2001;344:573–9.
- 30 Nogee LM, deMello DE, Dehner LP, et al. Deficiency of pulmonary surfactant protein B in congenital alveolar proteinosis. *N Engl J Med* 1993;328:406–10.
- 31 Van Moersel CHM, van der Vis JJ, Grutters JC. Genetic disorders of the surfactant system: focus on adult disease. *Eur Respir Rev* 2021;30:200085:30.
- 32 DeBoer EM, Liptzin DR, Humphries SM, et al. Ground glass and fibrotic change in children with surfactant protein C dysfunction mutations. *Pediatr Pulmonol* 2021;56:2223–31.
- 33 Dell SD, Schneider R, Yeung RSM. Pulmonary involvement in the systemic inflammatory diseases of childhood. In: Wilmott RW, Bush A, Detering RR, et al., eds. *Kendig's disorders of the respiratory tract in children*. Philadelphia, PA: Elsevier, 2019: 850–75.
- 34 Schütz K, Schmidt A, Schwärk N, et al. Variants in FGFI9 cause early onset of severe childhood interstitial lung disease: a detailed description of four affected children. *Pediatr Pulmonol* 2023;58:3095–105.
- 35 Thorwarth A, Schnittert-Hübener S, Schrupp P, et al. Comprehensive genotyping and clinical characterisation reveal 27 novel NKX2-1 mutations and expand the phenotypic spectrum. *J Med Genet* 2014;51:375–87.
- 36 Prapa M, Lago-Docampo M, Swietlik EM, et al. First genotype–phenotype study in tbx4 syndrome: gain-of-function mutations causative for lung disease. *Am J Respir Crit Care Med* 2022;206:1522–33.
- 37 Sheldermine SC, Semple T, Wallis C, et al. Filamin A (FLNA) mutation-A newcomer to the childhood interstitial lung disease (child) classification. *Pediatr Pulmonol* 2017;52:1306–15.
- 38 Shah AS, Black ED, Simon DM, et al. Heterogeneous pulmonary phenotypes in filamin A mutation-related lung disease. *Pediatr Allergy Immunol Pulmonol* 2021;34:7–14.
- 39 Huang H, Pan J, Spielberg DR, et al. A dominant negative variant of RAB5B disrupts maturation of surfactant protein B and surfactant protein C. *Proc Natl Acad Sci U S A* 2022;119:e2105228119.
- 40 Lenz D, Stahl M, Seidl E, et al. Rescue of respiratory failure in pulmonary alveolar proteinosis due to pathogenic MARS1 variants. *Pediatr Pulmonol* 2020;55:3057–66.
- 41 Enaud L, Hadchouel A, Coulomb A, et al. Pulmonary alveolar proteinosis in children on la réunion island: a new inherited disorder? *Orphanet J Rare Dis* 2014;9:85.
- 42 La Fay C, Hoebeke C, Juzaud M, et al. Deep phenotyping of MARS1 (interstitial lung and liver disease) and LARS1 (infantile liver failure syndrome 1) recessive multisystemic disease using human phenotype ontology annotation: overlap and differences. case report and review of literature. *Eur J Med Genet* 2021;64:104334.
- 43 Guo M, Yang XL, Schimmel P. New functions of aminoacyl-trna synthetases beyond translation. *Nat Rev Mol Cell Biol* 2010;11:668–74.
- 44 Schuch LA, Forstner M, Rapp CK, et al. FARS1-related disorders caused by bi-allelic mutations in cytosolic phenylalanyl-trna synthetase genes: look beyond the lungs! *Clin Genet* 2021;99:789–801.
- 45 Xu Z, Lo W-S, Beck DB, et al. Bi-allelic mutations in phe-trna synthetase associated with a multi-system pulmonary disease support non-translational function. *Am J Hum Genet* 2018;103:100–14.
- 46 Charbit-Henrion F, Foguy-Deschaumes R, Borensztajn K, et al. Systemic inflammatory syndrome in children with FARS1 deficiency. *Clin Genet* 2022;101:552–8.
- 47 Usimaja J, Kaarteenaho R, Paakkola T, et al. NHLRC2 variants identified in patients with fibrosis, neurodegeneration, and cerebral angiomas (FINCA): characterisation of a novel cerebropulmonary disease. *Acta Neuropathol* 2018;135:727–42.
- 48 Sczakiel HL, Zhao M, Wollert-Wulf B, et al. Broadening the phenotypic and molecular spectrum of FINCA syndrome: biallelic NHLRC2 variants in 15 novel individuals. *Eur J Hum Genet* 2023;31:905–17.
- 49 Rapp CK, Van Dijk I, Laugwitz L, et al. Expanding the phenotypic spectrum of FINCA (fibrosis, neurodegeneration, and cerebral angiomas) syndrome beyond infancy. *Clin Genet* 2021;100:453–61.
- 50 Kreus M, Lehtonen S, Hinttala R, et al. NHLRC2 expression is increased in idiopathic pulmonary fibrosis. *Respir Res* 2022;23:206.
- 51 Cabral DA, Canter DL, Muscal E, et al. Comparing presenting clinical features in 48 children with microscopic polyangiitis to 183 children who have granulomatosis with polyangiitis (wegener's): an archive cohort study. *Arthritis Rheumatol* 2016;68:2514–26.

- 52 Roszkiewicz J, Smolewska E. From fibrosis to diagnosis: a paediatric case of microscopic polyangiitis and review of the literature. *Rheumatol Int* 2018;38:683–7.
- 53 Marten K, Schnyder P, Schirg E, et al. Pattern-based differential diagnosis in pulmonary vasculitis using volumetric CT. *AJR Am J Roentgenol* 2005;184:720–33.
- 54 Palafox-Flores JG, Valencia-Ledezma OE, Vargas-López G, et al. Systemic lupus erythematosus in pediatric patients: pulmonary manifestations. *Respir Med* 2023;220:107456.
- 55 Veiga CS, Coutinho DS, Nakaie CMA, et al. Subclinical pulmonary abnormalities in childhood-onset systemic lupus erythematosus patients. *Lupus (Los Angel)* 2016;25:645–51.
- 56 Dai G, Li L, Wang T, et al. Pulmonary involvement in children with systemic lupus erythematosus. *Front Pediatr* 2020;8:617137.
- 57 Sabbagh S, Pinal-Fernandez I, Kishi T, et al. Anti-ro52 autoantibodies are associated with interstitial lung disease and more severe disease in patients with juvenile myositis. *Ann Rheum Dis* 2019;78:988–95.
- 58 Sato S, Kobayashi N, Yamazaki K, et al. Clinical utility of anti-CADM-140/ melanoma differentiation-associated gene 5 autoantibody titers in patients with juvenile dermatomyositis and rapidly progressive interstitial lung disease. *Arthritis Rheumatol* 2012;64:128.
- 59 Miyazaki E, Ando M, Muramatsu T, et al. Early assessment of rapidly progressive interstitial pneumonia associated with myopathic dermatomyositis. *Clin Rheumatol* 2007;26:436–9.
- 60 Foeldvari I, Torok KS. Review for best practice in clinical rheumatology juvenile systemic sclerosis - updates and practice points. *Best Pract Res Clin Rheumatol* 2021;35:101688.
- 61 Li JC, Tadros S, Rosser F, et al. Pulmonary nodules in juvenile systemic sclerosis: a case-series from the national registry for childhood onset scleroderma (NRCOS). *Diagnostics (Basel)* 2023;13:2103.
- 62 Vecé TJ, Watkin LB, Nicholas S, et al. Copa syndrome: a novel autosomal dominant immune dysregulatory disease. *J Clin Immunol* 2016;36:377–87.
- 63 Nguyen HN, Salzman R, Vogel TP, et al. Imaging findings of COPA syndrome. *Pediatr Radiol* 2023;53:844–53.
- 64 David C, Frémond M-L. Lung inflammation in STING-associated vasculopathy with onset in infancy (SAVI). *Cells* 2022;11:318.
- 65 Wang Y, Wang F, Zhang X. STING-associated vasculopathy with onset in infancy: a familial case series report and literature review. *Ann Transl Med* 2021;9:176.
- 66 Hengst M, Nachrich L, Mahavadi P, et al. Hermansky-pudlak syndrome type 2 manifests with fibrosing lung disease early in childhood. *Orphanet J Rare Dis* 2018;13:42.
- 67 Li W, Hao CJ, Hao ZH, et al. New insights into the pathogenesis of hermansky-pudlak syndrome. *Pigment Cell Melanoma Res* 2022;35:290–302.
- 68 El-Chemaly S, O'Brien KJ, Nathan SD, et al. Clinical management and outcomes of patients with hermansky-pudlak syndrome pulmonary fibrosis evaluated for lung transplantation. *PLoS One* 2018;13:e0194193.
- 69 O'Brien KJ, Introne WJ, Akal O, et al. Prolonged treatment with open-label pirfenidone in hermansky-pudlak syndrome pulmonary fibrosis. *Mol Genet Metab* 2018;125:168–73.
- 70 Velázquez-Díaz P, Nakajima E, Sorkhdini P, et al. Hermansky-pudlak syndrome and lung disease: pathogenesis and therapeutics. *Front Pharmacol* 2021;12:644671.
- 71 Young LR, Gulleman PM, Short CW, et al. Epithelial-macrophage interactions determine pulmonary fibrosis susceptibility in hermansky-pudlak syndrome. *JCI Insight* 2016;1:e88947.
- 72 Gothe F, Gehrig J, Rapp CK, et al. Early-onset, fatal interstitial lung disease in STAT3 gain-of-function patients. *Pediatr Pulmonol* 2021;56:3934–41.
- 73 Salehian S, Semple T, Pabary R. Childhood interstitial lung disease: short lessons from telomeres. *Thorax* 2021;76:1250–2.
- 74 Olivieri C, Mondino A, Chinello M, et al. Clinical heterogeneity in a family with DKC1 mutation, dyskeratosis congenita and hoeraal-hreidarsson syndrome in first cousins. *Pediatr Rep* 2017;9:7301.
- 75 Wawszczak M, Bielecka T, Szczukocki M. Hypersensitivity pneumonitis in children. *Ann Agric Environ Med* 2021;28:118830:214–9.
- 76 Griesse M, Rampf U, Hofmann D, et al. Pulmonary complications after bone marrow transplantation in children: twenty-four years of experience in a single pediatric center. *Pediatr Pulmonol* 2000;30:393–401.
- 77 Panoskaltis-Mortari A, Griesse M, Madtes DK, et al. An official american thoracic society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. *Am J Respir Crit Care Med* 2011;183:1262–79.
- 78 Lee YK, Huh R, Kim J, et al. Late-onset noninfectious interstitial lung disease following autologous hematopoietic stem cell transplantation in paediatric patients. *Respirology* 2016;21:1068–74.
- 79 Atag E, Bas Ikizoglu N, Gokdemir Y, et al. An adolescent with idiopathic pleuroparenchymal fibroelastosis. case report. *Arch Argent Pediatr* 2018;116:e147–50.
- 80 Oh S, Lee JW, Yoo S-Y, et al. Pleuroparenchymal fibroelastosis after hematopoietic stem cell transplantation in children: a propensity score-matched analysis. *Eur Radiol* 2023;33:2266–76.
- 81 Beynat-Mouterde C, Beltramo G, Lezmi G, et al. Pleuroparenchymal fibroelastosis as a late complication of chemotherapy agents. *Eur Respir J* 2014;44:523–7.
- 82 Seidl E, Schwerk N, Carlsen J, et al. Acute exacerbations in children's interstitial lung disease. *Thorax* 2022;77:799–804.
- 83 Wambach JA, Young LR. New clinical practice guidelines on the classification, evaluation and management of childhood interstitial lung disease in infants: what do they mean? *Expert Rev Respir Med* 2014;8:653–5.
- 84 Kurland G, Deterding RR, Hagood JS, et al. American Thoracic Society committee on childhood interstitial lung disease, the chILDRN. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Respir Crit Care Med* 2013;188:376–94.
- 85 Griesse M, Seidl E, Hengst M, et al. International management platform for children's interstitial lung disease (child-EU). *Thorax* 2018;73:231–9.
- 86 Nathan N, Berdah L, Delestrain C, et al. Interstitial lung diseases in children. *Presse Med* 2020;49:103909.
- 87 Drummond D, Thumerelle C, Reix P, et al. Effectiveness of palivizumab in children with childhood interstitial lung disease: the french experience. *Pediatr Pulmonol* 2016;51:688–95.
- 88 De Souza FHC, De Araújo DB, Hoff LS, et al. Diagnosis and treatment of interstitial lung disease related to systemic autoimmune myopathies: a narrative review. *Reumatismo* 2023;75.
- 89 Sanchez GAM, Reinhardt A, Ramsey S, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest* 2018;128:3041–52.
- 90 Krutke S, Rietschel C, Horneff G. Baricitinib in therapy of COPA syndrome in a 15-year-old girl. *Eur J Rheumatol* 2020;7:S78–81.
- 91 Frémond M-L, Legendre M, Fayon M, et al. Use of ruxolitinib in COPA syndrome manifesting as life-threatening alveolar haemorrhage. *Thorax* 2020;75:92–5.
- 92 Jordan S, Distler JHW, Maurer B, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the european scleroderma trial and research (EUSTAR) group. *Ann Rheum Dis* 2015;74:1188–94.
- 93 Sircar G, Goswami RP, Sircar D, et al. Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. *Rheumatology (Oxford)* 2018;57:2106–13.
- 94 Daoussis D, Melissaropoulos K, Sakellaropoulos G, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum* 2017;46:625–31.
- 95 Zulian F, Dal Pozzolo R, Meneghel A, et al. Rituximab for rapidly progressive juvenile systemic sclerosis. *Rheumatology (Oxford)* 2020;59:3793–7.
- 96 Griesse M, Kappler M, Stehling F, et al. Randomized controlled phase 2 trial of hydroxychloroquine in childhood interstitial lung disease. *Orphanet J Rare Dis* 2022;17:289.
- 97 Deterding R, Young LR, DeBoer EM, et al. Nintedanib in children and adolescents with fibrosing interstitial lung diseases. *Eur Respir J* 2023;61:2201512.
- 98 Maher TM, Brown KK, Cunningham S, et al. Estimating the effect of nintedanib on forced vital capacity in children and adolescents with fibrosing interstitial lung disease using a bayesian dynamic borrowing approach. *Pediatr Pulmonol* 2024;59:1038–46.
- 99 Forstner M, Lin S, Yang X, et al. High-content screening identifies cyclosporin a as a novel ABCA3-specific molecular corrector. *Am J Respir Cell Mol Biol* 2022;66:382–90.
- 100 Sitaraman S, Alysandratos K-D, Wambach JA, et al. Gene therapeutics for surfactant dysfunction disorders: targeting the alveolar type 2 epithelial cell. *Hum Gene Ther* 2022;33:1011–22.
- 101 Alysandratos K-D, Russo SJ, Petcherski A, et al. Patient-specific ipscs carrying an SFTPC mutation reveal the intrinsic alveolar epithelial dysfunction at the inception of interstitial lung disease. *Cell Rep* 2021;36:109636.