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Letter to the Editor

Novel antivirals for severe enterovirus infection in immunocompromised hosts; A case series

Previously in this Journal, it was pointed out that novel antiviral treatments are badly needed for severe enterovirus infections.[1] We describe eight immunocompromised individuals who received antiviral combinations with novel and repurposed agents in UK (Table 1).

Enteroviruses (EV) are RNA viruses that cause self-limiting or asymptomatic infection in immunocompetent individuals. However sepsis-like syndrome, chronic neurological disease, and mortality may occur in neonates and immunocompromised patients, particularly with antibody deficiencies.[1,2] There are still no licenced agents to treat severe EV disease and to our knowledge no phase 3 trials are in progress.

Antiviral agents were used on ad hoc basis in this case series. Patients were retrospectively identified by clinicians providing expert advice on the use of novel antivirals. Patients or their legal guardian gave written consent for publication through their treating physician. A standardized data set was supplied for every patient. One patient has been previously reported.[3]

Patients were aged between 5 days and 34 years and presented with subacute meningoencephalitis (6/8) or sepsis (2/8). Patients 1–4 were moderately immunocompromised due to prematurity or immunosuppressive therapy (IST). Patients 5–8 were profoundly immunocompromised due to haematopoietic stem cell transplant (HSCT), gene therapy or IST with an underlying primary immunodeficiency (PID). Three patients initially received steroids for a presumed inflammatory condition, all subsequently deteriorated.

At presentation, fever (5/8), hypothermia (1/8) and weight loss (1/8) with organ dysfunction were reported. Neurological features were common and wide ranging, particularly lethargy or drowsiness (4/8) and brain stem signs (4/8). Both preterm infants had a sepsis-like syndrome.

EV diagnosis was made 3 days to 10 months after symptom onset. Lumbar puncture (LP) was performed in 6/8 patients. EV CSF PCR was positive in all 6 cases, although in patients 5 and 6 EV PCR was first positive on the third LP. In patient 5, in whom EV PCR was only positive at high cycle threshold, Coxsackievirus B4 was clearly demonstrated on brain biopsy through metagenomics. Here, metagenomic sequencing was shown to identify EV infection where conventional PCRs had been unsuccessful.[4,5] EV protein was confirmed by immunohistochemistry staining in several neuron-like cells (Fig. 1).

MRI brain demonstrated typical EV changes in the thalami, cerebellum, pons, periventricular white matter and basal ganglia in 4/6,[6] but normal findings were seen in 2/6 despite clinical evidence of neurological dysfunction and abnormal CSF. B and/or T cell lymphopenia was found in 6/6 patients and hypogammaglobulinemia in 5/6 at time of EV diagnosis.

All patients received high dose IVIG (1–4 g/kg/month). Half initially received IVIG alone or with fluoxetine, with other novel antivirals added later. The others started treatment with IVIG and novel antivirals or ribavirin at the same time. Pocapavir (5/8), fluoxetine (6/8), favipiravir (5/8), nitazoxanide (4/8), and ribavirin (2/8) were used in varying combinations.

Novel antivirals were started in four patients within 12 days of symptom onset. The interval for patients four, five and six was 1.2–3 months, and 52 months for patient three.

The duration of therapy varied from 14 days to more than 4 years in patient three who remains persistently EV CSF positive. One patient died before EV CSF clearance. All others cleared EV within 2–17 weeks. No severe adverse effects were reported.

Initial therapy with IVIG alone was associated with deterioration in 2/3 (patient 4 and 6) but significant improvement in 1/3 (patient 7).

Complete recovery without neurological sequelae was seen in 2/8 patients. In both instances, diagnosis of EV infection and initiation of antiviral treatment occurred within 12 days of symptom onset. Significant clinical improvement was observed in 4/8. Two patients died: one from multiorgan failure on day 5 of EV infection, the other 18 months after symptom onset due to severe neurological deterioration despite clearance of EV on day 13 after starting Nitazoxanide.

This small case series provides support for IVIG and early combination antiviral therapy in significantly immunosuppressed individuals with severe EV disease. In our cohort, prompt diagnosis and therapy were associated with better outcomes.

We used novel antivirals that are known to have in vitro activity against EV. Due to the risk of drug resistance, pocapavir[2] and fluoxetine[7] were used in combination, except in both preterm neonates where pharmacokinetic/pharmacodynamic data are scarce.

Pocapavir inhibits EV capsid disassembly, preventing release of viral RNA into the host cell. Successful pocapavir treatment has been reported in neonatal EV myocarditis, vaccine-derived poliovirus infection in X-linked agammaglobulinemia and EV meningoencephalitis.[2,8] Fluoxetine, a selective serotonin reuptake inhibitor, specifically inhibits EV replication by binding the viral 2C protein.[7] Reports of efficacy are mixed with one retrospective case series finding little benefit in children with EV acute flaccid myelitis.[9] Favipiravir has broad spectrum anti RNA dependent RNA polymerase activity, including against EV.[10]

Delay in initiating novel antivirals occurred in half of our cohort, primarily due to challenges of diagnosing EV infection. These findings should encourage clinicians to submit repeated samples from multiple biological compartments to increase the yield of EV detection. Invasive tissue sampling and testing using metagenomics should be considered if diagnostic uncertainty remains.

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Table 1
Detailed description of eight patients with severe enterovirus infection.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8*
Demography								
Gender	female	female	female	male	male	male	female	male
Underlying condition	prematurity (35+6w)	prematurity (35+6w)	connective tissue disorder[a], ITP	multiple sclerosis	β-Thalassaemia major	MHC class II deficient SCID[b]	AA; aGvHD[c], EBV-viraemia	X-linked gamma chain SCID[d]
Immunosuppressive therapy	none	none	steroids, Ritux, AZA, MMF	dimethyl fumarate, Ocrelizumab	HSCT[e]	steroids	Haplo-HSCT[f], steroids[g], Ritux[h]	lentiviral gene therapy[i]
Age at symptom onset of EV inf.	5th d of life	5th d of life	34y	30y	2y	24m	13y	8m
Time from 1st symptoms to EV dx	3d	3d	10m	2.5m	27d	37d	3d	10d
Clinical picture at diagnosis of EV infection								
Neurological involvement (times given after first presentation)	lethargy	none	myeloradiculopathy with brisk reflexes m +5 myofasciitis, mild neuropathy, hearing loss m +10 severe peripheral neuropathy, deafness, confusion	dizziness, lethargy, autonomic dysfunction, ataxia, shaking hands, left-side-weakness, slurred speech, double vision	drowsiness d +27 somnolence, mute, dysphagia d +42 paraplegy, clones	floppy, unsteady, shuddering movements, drowsy, not talking, abnormal eye movements m +1 more unwell, neck stiffness, gross dystonia and dyskinesia	dysphagia, disorientation, aggressive behaviour	bilateral squint, inability to fix and follow, up gazing episodes, limb dyskinesia, dystonic movements, truncal hypotonia
Other manifestations of EV infection	sepsis with DIC, hypothermia, respiratory, liver, intestinal failure, impaired insulin production	sepsis with DIC, NEC	m+4 fever, cough m+11 myocarditis (ECHO: EF 25%)	fever, bovine cough, weight loss, night sweets	fever	fever, cough, increased work of breathing, diarrhoea (multi-microbial)	fever, mild upper respiratory tract inf. 1w ago, retinal hemorrhages	none
Imaging at diagnosis of EV infection								
MRI head	not done	not done	normal	rhombencephalitis, extension of known pontine MS lesions new lesions subcortical, periventricular, cerebellar	FLAIR hyperintensity subcortical white matter, left thalamus, pons, cerebellar	T2 hyperintensity mainly cerebellum, pulvinar/thalami paramedian bilateral, diffuse oedema	normal	T2 hyperintensity thalami + brainstem with restricted diffusion, no enhancement
CSF, evidence of EV, lymphocyte subsets and immunoglobulins at diagnosis of EV infection								
CSF WCC x10^6/L	not done	not done	48 (100% lymph)	<3	8 (100% lymph)	2	105 (90% lymph)	23
CSF protein (g/L)	not done	not done	0.9 (↑)	0.94 (↑)	3.2 (↑)	0.21 (n)	0.51 (↑)	1.06 (↑)
EV in CSF (ct)	not done	not done	pos.	pos.	pos.(39)[j],neg d1,13 after 1st symptoms	pos.(32),neg d1,16 after 1st symptoms	pos.	pos. (38)
EV in blood (ct)	pos. (23)	pos.	neg.	neg.	neg.	neg.	pos.	neg.
EV in NPA (ct)	pos. (23)	n.a.	neg.	pos. (24)	n.a.	thr. swap pos. (31)	neg.	pos. (22)
EV in stool (ct)	pos. (32)	n.a.	neg.	rect. swap pos.(24)	neg.	pos. (26)	neg.	pos. (35)
EV - genotype	n.a.	n.a.	Echovirus 3	Coxsackie B5	Coxsackie B4	Coxsackie B5	n.a.	Coxsackie B1
lymphocyte subsets – absolute count in x10^6/L (normal range)	CD19+ 0.303 (0.315 - 1.383) CD3+ 0.904 (3.18 - 5.401) CD4+ 0.801 (2.33 - 3.617) CD8+ 0.125 (0.712-1.361)	n.a.	CD19+ 0 (0.1 - 0.5) CD3+ 0.98 (0.7 - 2.1) CD4+ 0.65 (0.3 - 1.4) CD8+ 0.33 (0.2 - 0.9)	severe pan-lymphopenia -total lymphocytes 0.2	n.a.	CD19+ 0.37 (0.733 - 1.338) CD3+ 0.19 (2.542 - 4.933) CD4+ 0.10 (1.573 - 2.949) CD8+ 0.012 (0.656 - 1.432)	CD19+ 0 (0.173 - 0.685) CD3+ 0.87 (0.954 - 2.332) CD4+ 0.70 (0.61 - 1.446) CD8+ 0.19 (0.282 - 0.749)	CD19+ 4.09 (0.776 - 2.238) CD3+ 0.04 (2.284 - 4.776) CD4+ 0.02 (1.523 - 3.472) CD8+ 0 (0.524 - 1.583)
IgG (normal range)	n.m. before IVIG	n.a.	normal	n.m. before IVIG	n.m. before IVIG	5.3 (3.5-10) g/L	0.8 (7-14) g/L	n.m. before IVIG
IgM (normal range)	0.7 (0.1–0.2) g/L	n.a.	<0.2 (0.5-1.9) g/L	0.1 (0.5-1.9) g/L	↓ (exact value n.a.)	0.36 (0.4-1.4) g/L	<0.7 (0.7-1.5) g/L	<0.05 (0.3-1.0) g/L
IgA (normal range)	0.53 (0–0.2)	n.a.	1.2 (0.8-2.8) g/L	0.53 (0.8-2.8) g/L	↓ (exact value n.a.)	<0.05 (0.3-1.2) g/L	0.04 (0.7-2.3) g/L	<0.07 (0.3-1.4) g/L
EV treatment details								
Treatment of EV infection	IVIG 1g/kg, once Pocapavir 25 mg/kg/d, 14d	IVIG 1g/kg, once Pocapavir 25 mg/kg/d, 2d	IVIG[k,l] 1 g/kg/28d, >4y Fluoxetine[k] 20 mg OD, >4y Favipiravir[k] 1200mg BD, >10m Nitazoxanide[k] 500 mg BD, >5m Pocapavir 1600 mg OD, 14 d	IVIG[k] 2 g/kg/28d, >6m Fluoxetine[k,m] 60 mg OD, >5m Ribavirin[k,n] 400 mg BD, 7d Nitazoxanide 500 mg BD, >5m Favipiravir[k] 600-1200mg BD, >5m Pocapavir 1600 mg OD, 14d	IVIG 5.75m Fluoxetine 4.75m Ribavirin 5m	IVIG[k,o] 0.5 g/kg/7d, 5m Fluoxetine[k] 9 mg OD, 12m Nitazoxanide[k] 250 mg BD, 12m Favipiravir[k,p] 200 mg BD to 400 mg TDS, 12m Pocapavir 750 mg/d, 14d	IVIG[k] 2g/kg/14d Favipiravir[q] 800 mg BD, 3w Nitazoxanide[k] 100 mg BD, 3w Fluoxetine 10 mg OD, 3w	IVIG[r] 1 g/kg/7d, 7m Fluoxetine[s] 5 mg OD, 6m Favipiravir[t] 200 mg TDS, 6m

(*continued on next page*)

Table 1 (*continued*)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8*
EV treatment details								
Time from 1st symptoms to IVIG	3d	3d	11m (regular) (once in m0)	2.5m	93d	9d	6d	11d
Time from 1st symptoms to Fluoxetine	-	-	11m	3m	102d	39d	12d	11d
Time from 1st symptoms to novel antivirals (F/N/P),R	3d (P)	3d (P)	52m (F, P) 59m (N)	3m (N, R) 3.25m (F) 6.75m (P)	93d (R)	37d (N) 44d (F) 115d (P)	12d (F, N)	11d (F)
Side effects of EV treatment	none	none	discoloration of urine, sticky eyes	transaminitis w/ ALT max. 237 U/l, normalised after pausing F and reintroduction at a lower dose	Ribavirin induced haemolysis, rbc tx required twice	transaminitis w/ ALT max. 88 U/l, normalised after pausing F and reintroduction at a lower dose	neutropenia, loss of appetite, neutrophil recovery within weeks after stopping all antivirals	none
Course of EV infection								
Clinical course after starting antiviral therapy	requiring ICU for 24d, mechanical ventilation for 21d, inotropes 8d in total	multiorgan failure on 10th day of life despite ICU, mechanical ventilation, and inotropes for 5d	m after starting IVIG + Fluoxetine: m +9: ongoing neuropathy, cognitive/ memory problems; myocarditis better m +26 neuropathy improved, reflexes returned, neurophysiology normal, cognitive improved, new headaches m +35 severe headaches, visual blurring, neck stiffness, better after large volume blood patch m +40 worsening balance, decrease in R-ODS score, no headaches	d after IVIG start: d +9 not following instructions, less communicative d after R/N start: d+9 better, move head to the speaking person, able to use communication cards d+19 responding to simple questions d+37 no confusion d+44 no word finding difficulties, full grammatical sentences; severe spastic dysarthria, improved intelligibility d +138 upper limb control, cognitive function improved	Within 2w, fever settled, he became responsive, less clonus. Within 3-4w, he regained cognitive function but remained paraplegic and unable to swallow	Within 1w fever, respiratory inf. settled, dystonia, dyskinesia medical controlled with difficulty over time. For 3-4m stable, intensive rehab, responsive, some head control ≥m+5 severe, neurological decline m +16 palliative, minimal function, rarely smiles or vocalises, not fixing/ following, hypotonic, brainstem dysfunction with episodes of sudden cardio-respiratory deterioration	d after starting IVIG: d +2-4 improvement with reorientation and normal swallowing d5: back to normal	w+4 neurological progress plateaued with intermittent dystonia, evolving hypertonia, ongoing developmental regression with no longer purposefully reaching for objects, or vocalising, but better head control and improved eye movement disorder w+6 significant ongoing dyskinesias w+8 some ongoing dystonic posturing, but no prolonged dystonic events
Time to neurological stabilisation after start of novel antivirals	n.a.	not reached	2y	9d	2w	not reached	5d after 1st IVIG / before starting novel antivirals	4w
MRI/CT head after starting antivirals	MRI d +37: global white matter abnormality, periventricular white matter calcification	not done	m after starting IVIG+ Fluoxetine: MRI m +5 normal CT m +26 ventricular enlargement, uncal herniation MRI m +35 brainstem anatomical distortion, slumping of mid-brain and 3rd ventricle CT m +50 (m +9 after P, F start) unchanged	MRI d+12 after starting IVIG: possible new cerebellum lesion MRI m+3 after starting N: multiple lesions without contrast enhancement, some less swollen	MRI m +2: leukoencephalopathy	MRI d+13 cerebral, cerebellar atrophy, less conspicuous T2 hyperintense changes within the posterior fossa and deep grey nuclei MRI m +3 unchanged MRI m +12 extensive atrophy cerebellar, progressive destruction, atrophy in frontal and parietal lobes	MRI d+42 normal	MRI d +48 increase in diffuse cerebral and cerebellar volume loss, residual signal changes both thalami, multifocal periventricular and deep white matter distribution, no new lesions
Time to clearance of EV	36d (P) (CSF)	n.a.	not cleared	4.25m (N, R)/ 19d (P) (CSF)	4.25m (R) (CSF)	13d (N) (CSF)	42d (F, N) (CSF, blood)	48d (F) (CSF)
Time of last CSF post F/N/P/R start	not done	not done	m +10 (F, P)	m +5.25 (N, R)	m +4.25 (R)	m +3 (F)	d +42 (F, N)	m +4 (F)
Last CSF WCC	not done	not done	32 x 10^6/L	17 x10^6/L	n.a.	4 x 10^6/L	24 x 10^6/L	3 x 10^6/L
Last CSF protein	not done	not done	1.82 g/L (↑)	1.52 g/L (↑)	n.a.	0.18 g/L (n)	0.46 g/L (↑)	0.3 g/L (n)
EV in last CSF	not done	not done	pos.	neg	neg	neg	neg	neg
Outcome								
FU after EV dx	10m	0.2m	62m	6m	9m	18m	3m	35m
Clinical outcome at last FU	alive w/o sequelae	died on d +5 of EV infection due to multi-organ failure	alive, relevant improved, residual sensorimotor neuropathy, ankle weakness, gait mild unsteady, mild cognitive impairment, fatigue, headaches, cochlear implants for deafness	alive, significant improved, good comprehension, dysarthria but able to communicate, supported walking	alive with ongoing neurological sequelae	died at home after progredient neurological deterioration with brainstem dysfunction	alive w/o sequelae	alive, supported sitting, not crawling, improved dystonia, limb hypertonia, non-verbal, can fix and follow, intermittent alternating convergent squint

Abbr, abnormal values in blue; AA, aplastic anemia; aGvHD, acute GvHD; ALT, Alanine Aminotransferase; AZA, azathioprine; BD, twice a day; CSF, cerebrospinal fluid; CT, computer tomography; ct, cycle threshold; d, day(s); DIC, disseminated intravascular coagulation; dx, diagnosis; EBV, Epstein-Barr-Virus; ECHO, echocardiography; EF, ejection fraction; EV, enterovirus; F, favipiravir; FLAIR, fluid-attenuated inversion recovery; FU, follow-up; GvHD, graft versus host disease; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; Ig, immunoglobulin; inf., infection; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin G; lymph, lymphocytes; m, month(s); max, maximal; MHC, major histocompatibility complex; MMF, Mycophenolate mofetil; MRI, magnet resonance imaging; MS, multiple sclerosis; n, normal; N, nitazoxanide; n.a., not available; NEC, necrotizing enterocolitis; neg., negative; n.m., not measured; NPA, nasopharyngeal aspirate; OD, once daily; P, pocapavir; pos., positive; R, ribavirin; rbc tx, red blood cell transfusion; Ritux, Rituximab; R-ODS, Rasch-built overall disability score; rect., rectal; SCID, severe combined immunodeficiency; TDS, three times a day; thr., throat; w, week(s); WCC, white cell count; w/o, without; y, year(s); ↑ increased, ↓ reduced, *published previously (3), [a]anti-Ro, -La pos., [b]Regulatory Factor X Associated Ankyrin Containing Protein (RFXANK) mutation, [c]skin and gut, [d]Interleukin 2 Receptor Subunit Gamma (IL2RG) mutation, [e]10/10 Matched family donor, condition Anti-thymocyte globulin, Fludarabine/Treosulfan/ Thiotepa, GvHD prophylaxis: Cyclosporin, [f]donor: mother, condition Anti-thymocyte globulin, Fludarabine, Cyclophosphamide, total body irradiation; GvHD prophylaxis: MMF+ Sirolimus [g]treatment for acute skin and gut GvHD, [h]as EBV treatment, [i]condition low-dose Busulfan [j]metagenomics on brain biopsy also pos., [k]ongoing, [l]2 g/kg/28d for the first 3 m, [m]20 mg OD, increased over 14d to 60 mg OD, [n]stopped at favipiravir start, [o]then subcutaneous 0.125 g/kg/7d, > 4 m, [p]800 mg BD on day 1, [q]1800 mg BD on day 1, [r]reduced to 1 g/kg/28d for 3 m, [s]initially 2.5 mg OD, [t]1200 mg on day 1

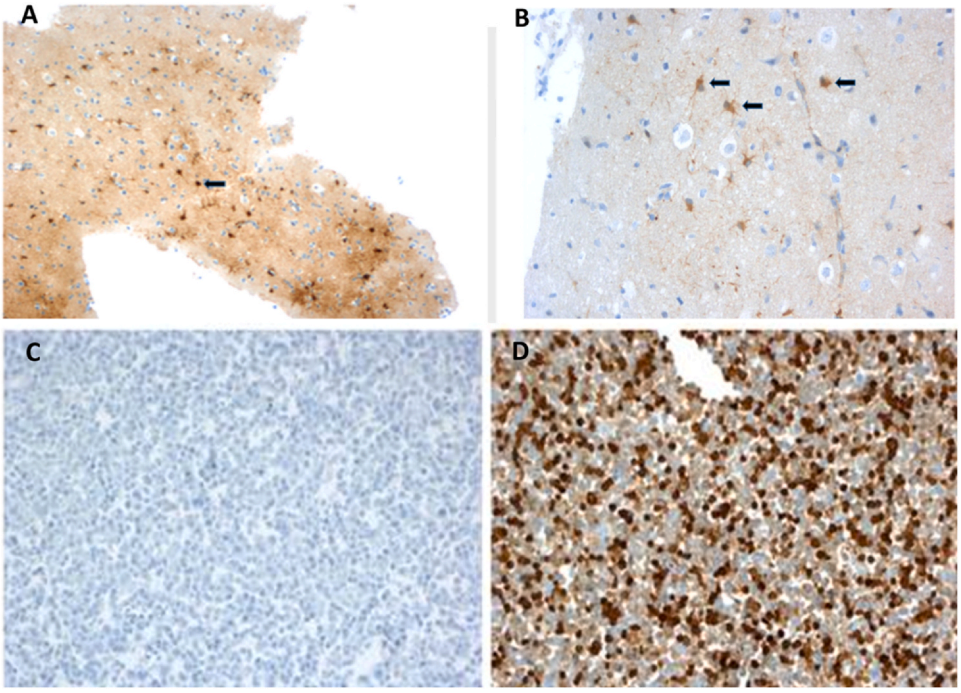

Fig. 1. Immunohistochemistry for EV VP1 (viral capsid protein 1) in brain biopsy in patient 5 (A, B) and in non-infected (C) and CVB1-infected (D) A 549 cells. A: 100x magnification; B-D: 200x magnification. A, B: Cells positive for EV VP1 stain dark brown showing a typical neuron-like morphology. Examples marked by arrows. C: Negative control. D: Positive control. Cells positive for VP1 stain dark brown.

There is a lack of robust data to justify routine use of novel and combination antiviral therapies in EV infection. Our case series, despite limitations including a small and heterogeneous cohort, retrospective observational design, and limited follow-up, suggests benefit of early combination antiviral therapy in heavily immunocompromised patients with severe EV disease. A high degree of suspicion for enteroviral encephalitis in deteriorating immunocompromised patients and early diagnosis with low threshold for brain biopsy where CSF PCR is inconclusive are paramount. Case by case discussion with a multidisciplinary team experienced in novel antivirals is warranted. Clearance of EV is likely to depend on reconstitution of immune recovery with antivirals acting as a bridging therapy in immunocompromised patients. Further descriptive studies, registry data enabling longitudinal follow-up and ultimately pragmatically designed RCTs are necessary to better define the efficacy, safety, and optimal combination of antiviral regimens for serious enteroviral infection.

Author contributions

A.M., L.R., J.B., S.K.: Conceptualization. **M.K., K.A.-A., S.A., L.F.A., I.B., C.B., K.C., J.E., S.F., C.M.G., S.G., R.D.H., J.H., H.H., A.Y.K., J.E.L., D.M.L., M.P.L., K.M., S.S., E.W., A.W., P.Y., L.Z., J.B., S.K.**: Acquisition of data and treatment of included patients. **M.K., D.M.L., J.B., S.K.**: Expert committee for treatment recommendations. **A.M., L.R., J.B., S.K.**: Writing original draft (lead). **M.K., K.A.-A., S.A., L.F.A., I.B., C.B., K.C., J.E., S.F., C.M.G., S.G., R.D.H., J.H., H.H., A.Y.K., J.E.L., D.M.L., M.P.L., K.M., S.S., E.W., A.W., P.Y., L.Z.:** Writing original draft (equal).

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