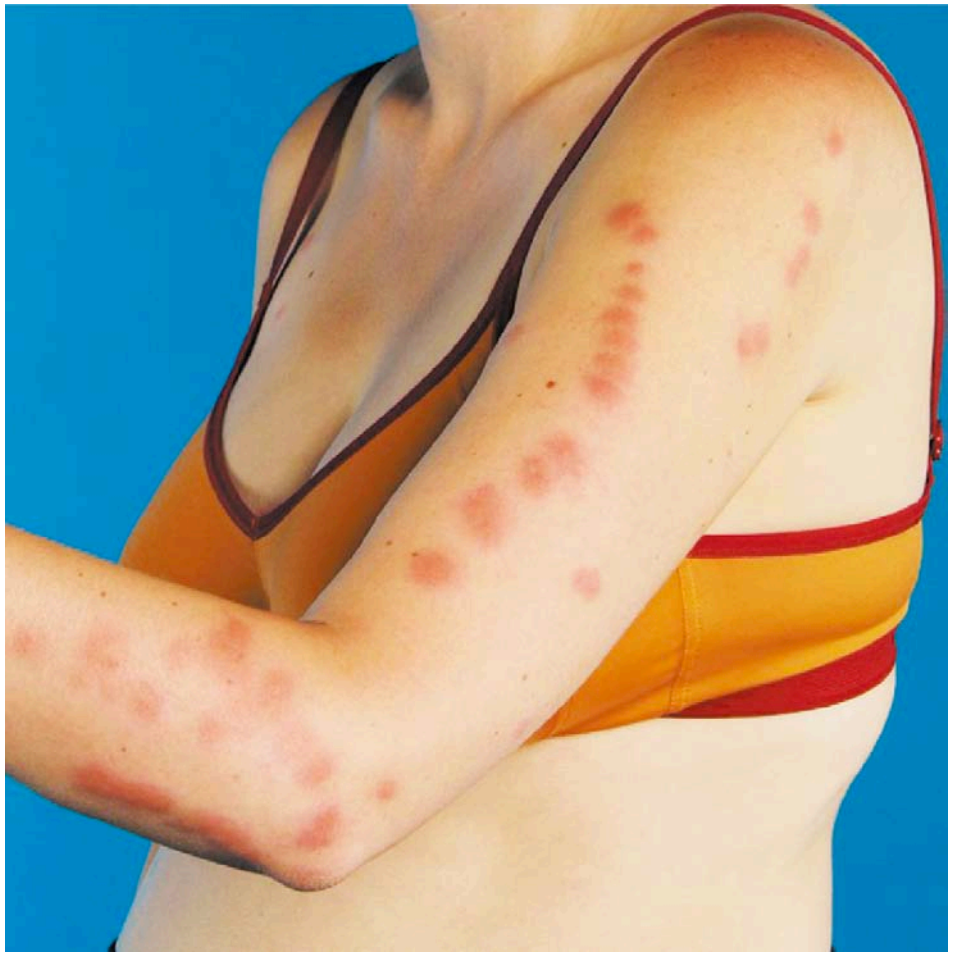


Bedbug bites

Dermatitis herpetiformis

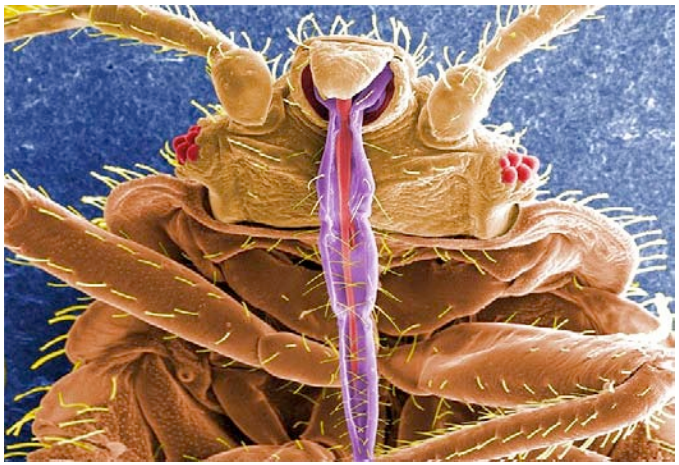
Ecthyma

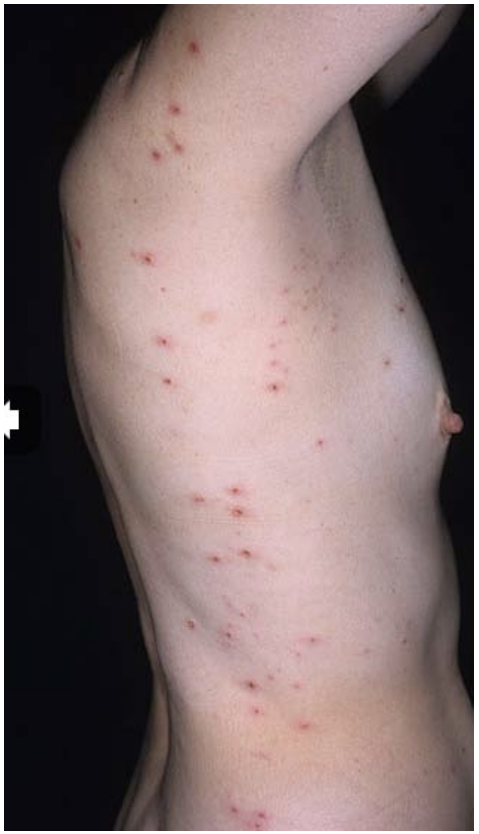
Guttate psoriasis

Lichen planus

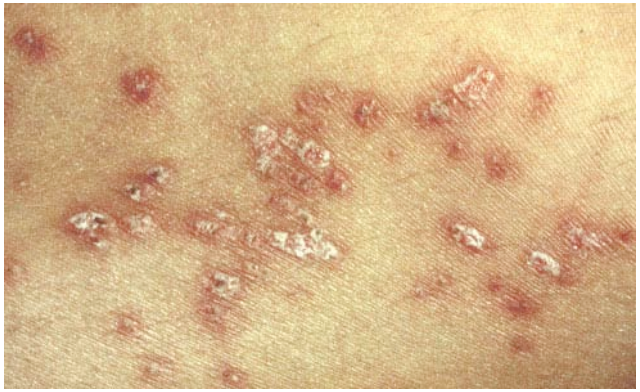
Bedbugs frequently attack exposed areas of the skin and are attracted to humans' high body temperature. Cutaneous reactions to bedbug bites are characterized by erythematous or urticarial papules. Lesions observed in a linear or cluster formation are typical. This patient's lesions responded to treatment with topical glucocorticoids.

Die Bettwanze (Cimex lectularius), auch Hauswanze, ist eine Wanze aus der Familie der Plattwanzen (Cimicidae). Diese sind darauf spezialisiert, in den Schlafplätzen von homoiothermen (gleichwarmen) Lebewesen – vor allem Menschen – zu leben und sich von deren Blut zu ernähren. Bettwanzen sind Zivilisationsfolger und gelten als klassische Parasiten. Die erwachsenen Tiere sind nur papierdünn und erreichen Körperlängen zwischen 3,8 und 5,5 Millimeter, im vollgesogenen Zustand bis zu 9 Millimeter. Die Bettwanze ist ein Kosmopolit. Sie ist im Norden bis etwas über den 65. Breitengrad beheimatet. In den Alpen kann sie bis fast 2000 m ü. NN vorkommen. In den Tropen und Subtropen kommen Populationen einer Unterart vor, die vormals als eigene Art C. hemipterus angesehen wurde.
Bettwanzen sind weitgehend an den Menschen und die ihn umgebenden Tiere gebunden. Sie leben in Städten, zum Teil in Wohnungen, die an die Brutplätze verwilderter Tauben angrenzen. Ferner halten sie sich in Ställen sowie in Säugerbauten und Vogelbruthöhlen im Freiland auf.

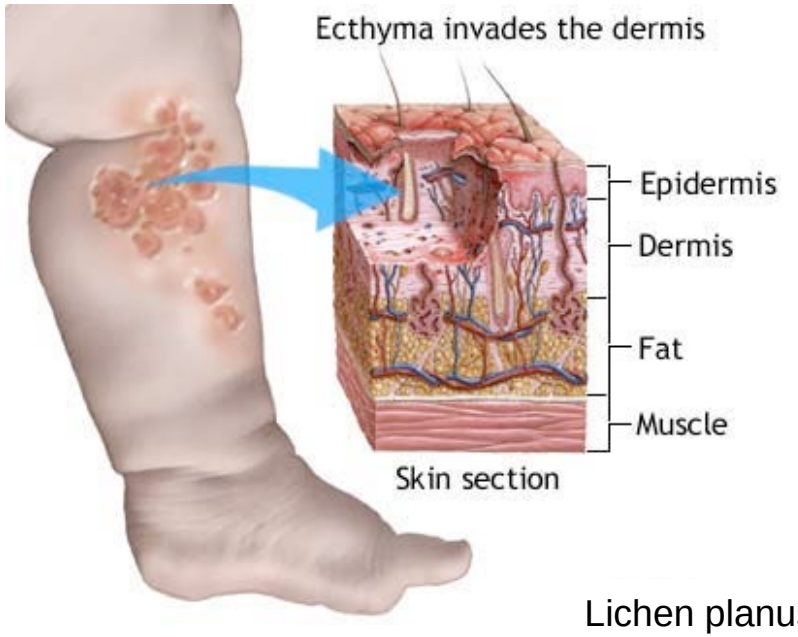




Dermatitis herpetiformes

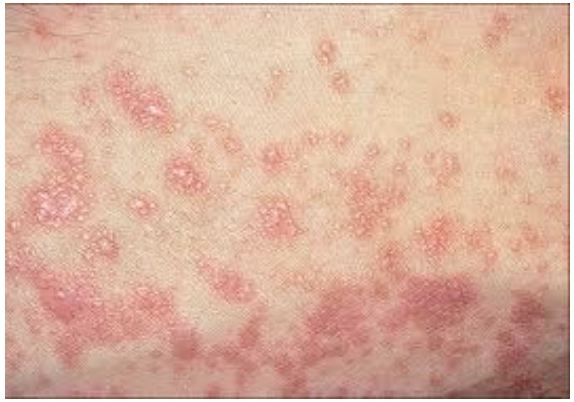


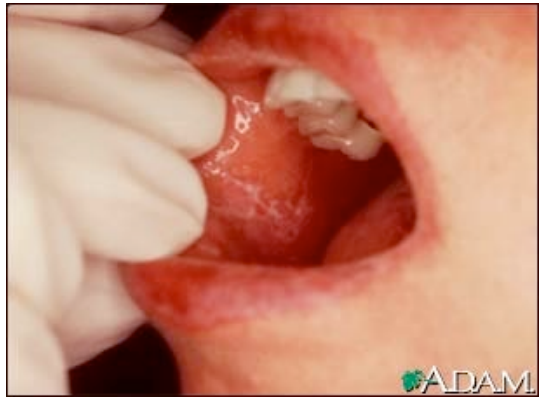
Guttate Psoriasis



Ecthyma is a skin infection similar to impetigo, but more deeply invasive. Usually caused by a streptococcus infection, ecthyma goes through the outer layer (epidermis) to the deeper layer (dermis) of skin, possibly causing scars.

Lichen planus



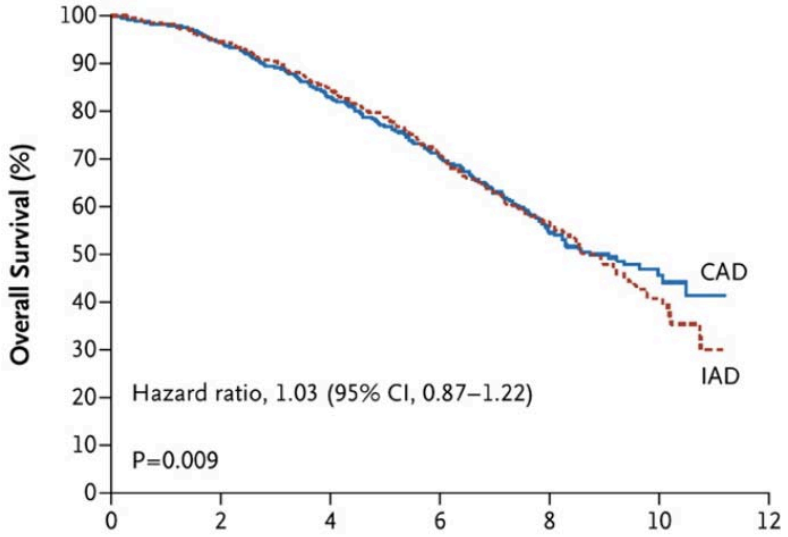


Oral lichen planus occurs in about half of the people who have lichen planus on their skin. It consists of painless, whitish streaks on the mucous membranes. This may also produce ulcers, which are usually painful.

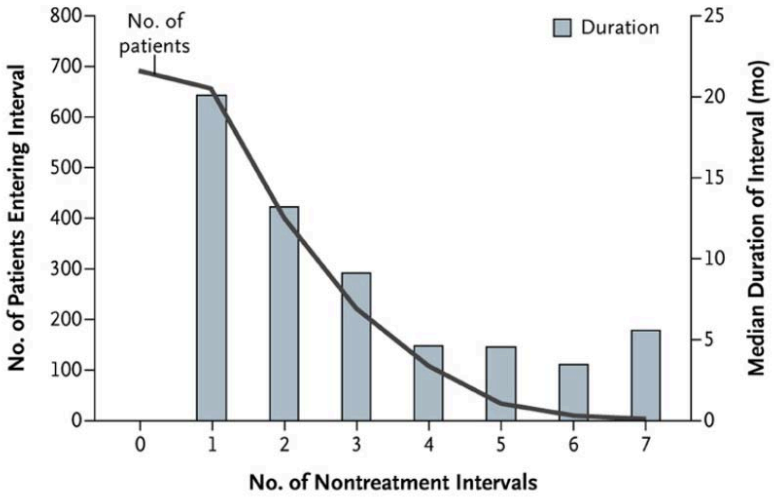
Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy

Intermittent androgen deprivation for prostate-specific antigen (PSA) elevation after radiotherapy may improve quality of life and delay hormone resistance. We assessed overall survival with intermittent versus continuous androgen deprivation in a noninferiority randomized trial. We enrolled patients with a PSA level greater than 3 ng per milliliter more than 1 year after primary or salvage radiotherapy for localized prostate cancer. Intermittent treatment was provided in 8-month cycles, with nontreatment periods determined according to the PSA level. The primary end point was overall survival. Secondary end points included quality of life, time to castration-resistant disease, and duration of nontreatment intervals.

Characteristic	Intermittent Therapy (N=690)	Continuous Therapy (N=696)	Total (N=1386)
Prior radical prostatectomy — no. (%)			
Yes	79 (11.4)	79 (11.4)	158 (11.4)
No	611 (88.6)	616 (88.5)	1227 (88.5)
Missing data	0	1 (0.1)	1 (0.1)
Time since radiotherapy — no. (%)			
1 to 3 yr	146 (21.2)	150 (21.6)	296 (21.4)
>3 yr	542 (78.6)	543 (78.0)	1085 (78.3)
Missing data	2 (0.3)	3 (0.4)	5 (0.4)
Baseline PSA level — no. (%)			
3–15 ng/ml	531 (77.0)	535 (76.9)	1066 (76.9)
>15 ng/ml	159 (23.0)	160 (23.0)	319 (23.0)
Missing data	0	1 (0.1)	1 (0.1)
Prior hormone therapy — no. (%)			
No	419 (60.7)	424 (60.9)	843 (60.8)
Yes	271 (39.3)	271 (38.9)	542 (39.1)
Age — yr			
Median	74.2	74.4	74.2
Range	29.4–89.7	45.3–88.9	29.4–89.7
ECOG performance status — no. (%)†			
0	548 (79.4)	568 (81.6)	1116 (80.5)
1	142 (20.6)	127 (18.2)	269 (19.4)
Missing data	0	1 (0.1)	1 (0.1)
Malignant prostate — no. (%)‡			
No	517 (74.9)	503 (72.3)	1020 (73.6)
Yes	135 (19.6)	150 (21.6)	285 (20.6)



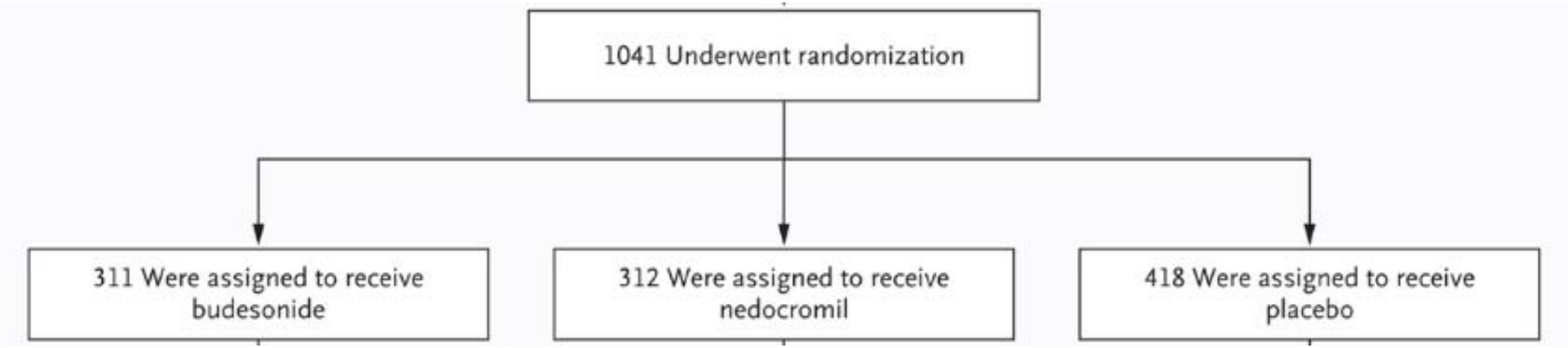
Cause	Deaths in Intermittent-Therapy Group (N=268)	Deaths in Continuous-Therapy Group (N=256)	Total Deaths (N=524)
		number (percent)	
Disease-specific			
Prostate cancer	110 (41.0)	87 (34.0)	197 (37.6)
Prostate cancer and off-protocol treatment	10 (3.7)	5 (2.0)	15 (2.9)
Complication of per-protocol treatment	0	2 (0.8)	2 (0.4)
Unrelated to prostate cancer			
Complication of off-protocol treatment*	2 (0.7)	5 (2.0)	7 (1.3)
Other primary cancer	59 (22.0)	54 (21.1)	113 (21.6)
Other cause	75 (28.0)	92 (35.9)	167 (31.9)



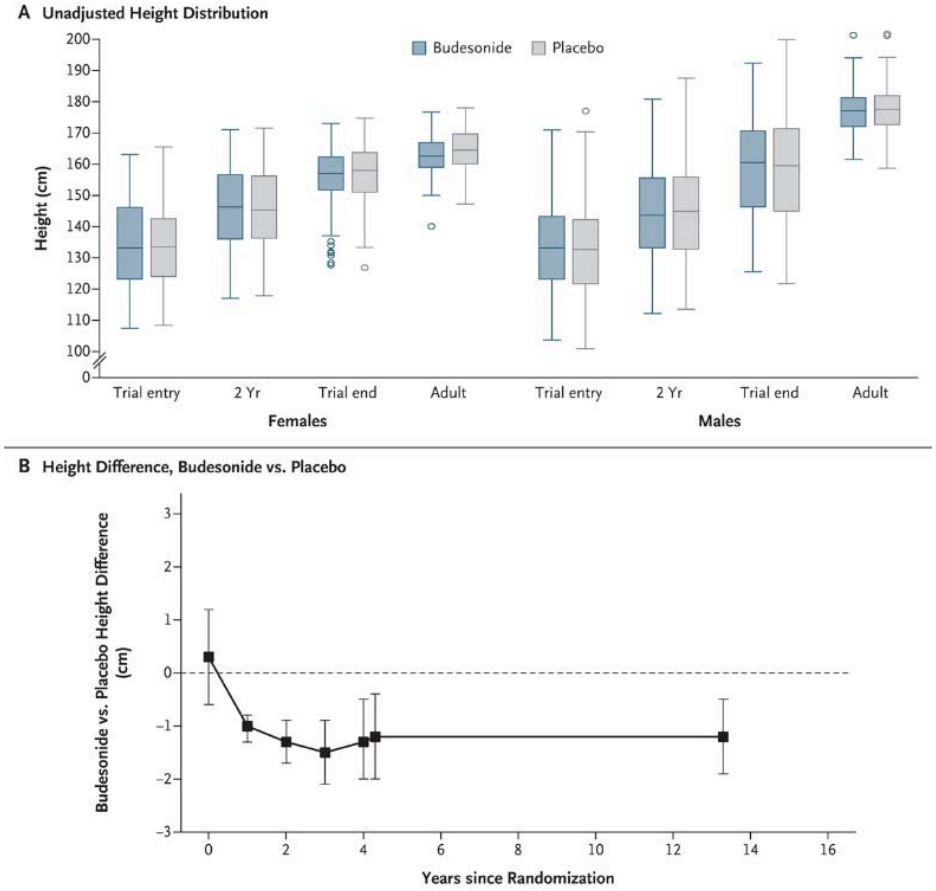
For functional domains (physical, role, and global health), the intermittent-therapy group had scores that were slightly better than those in the continuous-therapy group, but the differences were not significant. For items pertaining to symptoms, intermittent therapy was associated with significantly better scores for hot flashes ($P<0.001$), desire for sexual activity ($P<0.001$), and urinary symptoms ($P=0.006$), with a trend toward improvement in the level of fatigue ($P=0.07$). Intermittent androgen deprivation was noninferior to continuous therapy with respect to overall survival. Some quality-of-life factors improved with intermittent therapy.

Effect of Inhaled Glucocorticoids in Childhood on Adult Height

The use of inhaled glucocorticoids for persistent asthma causes a temporary reduction in growth velocity in prepubertal children. The resulting decrease in attained height 1 to 4 years after the initiation of inhaled glucocorticoids is thought not to decrease attained adult height. We measured adult height in 943 of 1041 participants (90.6%) in the Childhood Asthma Management Program; adult height was determined at a mean (±SD) age of 24.9±2.7 years. Starting at the age of 5 to 13 years, the participants had been randomly assigned to receive 400 µg of budesonide, 16 mg of nedocromil, or placebo daily for 4 to 6 years. We calculated differences in adult height for each active treatment group, as compared with placebo, using multiple linear regression with adjustment for demographic characteristics, asthma features, and height at trial entry.



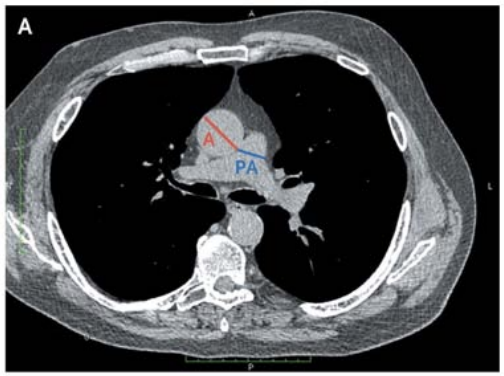
Variable	Mean Adult Height			Difference in Height			
	Budesonide (N=281)	Nedocromil (N=285)	Placebo (N=377)	Budesonide vs. Placebo (95% CI)	P Value	Nedocromil vs. Placebo (95% CI)	P Value
		cm		*cm*		*cm*	
All participants	171.1	172.1	172.3	−1.2 (−1.9 to −0.5)	0.001	−0.2 (−0.9 to 0.5)	0.61
Sex							
Female	162.8	163.9	164.6	−1.8 (−2.9 to −0.7)	0.001	−0.7 (−1.8 to 0.5)	0.26
Male	176.8	177.6	177.6	−0.8 (−1.8 to 0.2)	0.10	−0.0 (−0.9 to 0.9)	0.98
P value for interaction					0.10		0.49
Age at entry							
5–8 yr	170.7	171.8	172.6	−1.9 (−3.2 to −0.6)	0.004	−0.8 (−2.1 to 0.5)	0.22
9–13 yr	171.4	172.4	171.9	−0.5 (−1.7 to 0.6)	0.37	0.5 (−0.8 to 1.6)	0.48
P value for interaction					0.12		0.15



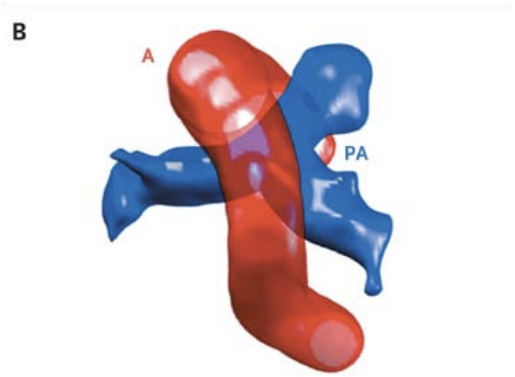
Mean adult height was 1.2 cm lower in the budesonide group than in the placebo group (P=0.001) and was 0.2 cm lower (95% CI, −0.9 to 0.5) in the nedocromil group than in the placebo group (P=0.61). A larger daily dose of inhaled glucocorticoid in the first 2 years was associated with a lower adult height (−0.1 cm for each microgram per kilogram of body weight) (P=0.007). The reduction in adult height in the budesonide group as compared with the placebo group was similar to that seen after 2 years of treatment. During the first 2 years, decreased growth velocity in the budesonide group occurred primarily in prepubertal participants. The initial decrease in attained height associated with the use of inhaled glucocorticoids in prepubertal children persisted as a reduction in adult height, although the decrease was not progressive or cumulative.

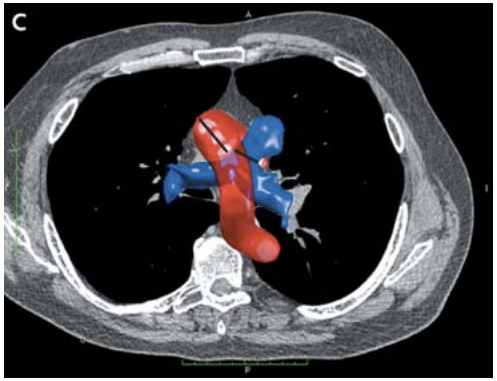
Pulmonary Arterial Enlargement and Acute Exacerbations of COPD

Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with accelerated loss of lung function and death. Identification of patients at risk for these events, particularly those requiring hospitalization, is of major importance. Severe pulmonary hypertension is an important complication of advanced COPD and predicts acute exacerbations, though pulmonary vascular abnormalities also occur early in the course of the disease. We hypothesized that a computed tomographic (CT) metric of pulmonary vascular disease (pulmonary artery enlargement, as determined by a ratio of the diameter of the pulmonary artery to the diameter of the aorta [PA:A ratio] of >1) would be associated with severe COPD exacerbations. We conducted a multicenter, observational trial that enrolled current and former smokers with COPD. We determined the association between a PA:A ratio of more than 1 and a history at enrollment of severe exacerbations requiring hospitalization and then examined the usefulness of the ratio as a predictor of these events in a longitudinal follow-up of this cohort, as well as in an external validation cohort. We used logistic-regression and zero-inflated negative binomial regression analyses and adjusted for known risk factors for exacerbation.



Panel A shows an axial chest computed tomographic (CT) image at the level of the left and right main pulmonary arteries, obtained without the administration of contrast material.



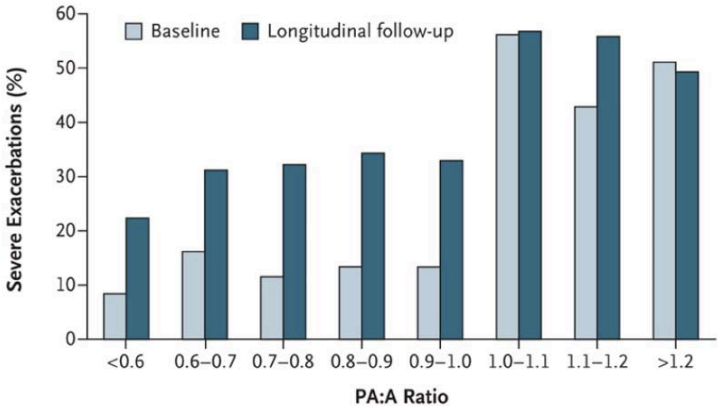


Panel B is a digital three-dimensional reconstruction, in axial cross section, of the great vessels that shows the spatial relationship between PA and A. In Panel C, the three-dimensional reconstruction is overlaid on the axial CT image.

Variable	PA:A Ratio ≤1 (N=2645)	PA:A Ratio >1 (N=819)	P Value
Age (yr)	64±9	63±9	0.003
Male sex (%)	60	42	<0.001
Non-Hispanic white race (%)†	81	67	<0.001
GOLD stage (%)‡			
II	56	43	<0.001
III	30	36	0.004
IV	14	21	<0.001
Body-mass index§	28±6	29±7	<0.001
Hypertension (%)	50	53	0.08
Asthma (%)	25	34	<0.001
Smoking history (pack-yr)	54±28	50±25	0.001
Current smoker (%)	43	36	<0.001
Congestive heart failure (%)	4	9	<0.001
Thromboembolic disease (%)	5	9	<0.001
Sleep apnea (%)	16	22	<0.001
Gastroesophageal reflux disease (%)	30	34	0.03
Supplemental oxygen use (%)	22	44	<0.001
Distance covered on 6-min walk (ft)	1204±415	983±450	<0.001
Total score on SGRQ¶	38±22	48±21	<0.001
Score on modified MRC‖	2±1	3±1	<0.001
FEV_1 (% of predicted value)	52±18	46±18	<0.001
FVC (% of predicted value)	78±17	73±18	<0.001
FEV_1:FVC ratio	0.50±0.13	0.48±0.13	<0.001
Diameter of aorta (cm)	3.27±0.38	3.09±0.35	<0.001
Diameter of pulmonary artery (cm)	2.75±0.37	3.33±0.42	<0.001
Percent of lung volume with emphysema on CT	12.6±12.5	14.0±13.1	0.01
Percent of lung volume with gas trapping on CT	38.7±20.7	40±20.6	0.14
Fourth-generation wall area percentage	65.5±2.4	66.2±2.2	<0.001
Frequency of exacerbations in previous year	0.59±1.09	1.21±1.48	<0.001

Time Period and Factor	Odds Ratio (95% CI)	P Value
History of severe exacerbations at enrollment		
FEV_1, per percentage-point decrease	1.02 (1.01–1.03)	0.001
SGRQ, per 1-point increase	1.03 (1.02–1.04)	<0.001
Age, per 1-year increase	0.97 (0.95–0.99)	0.002
PA:A ratio >1	4.78 (3.43–6.65)	<0.001
Severe exacerbations during longitudinal follow-up		
Exacerbation in previous yr	2.01 (1.61–2.49)	<0.001
FEV_1, per percentage-point decrease	1.02 (1.01–1.03)	<0.001
SGRQ, per 1-point increase	1.02 (1.01–1.02)	<0.001
GERD	1.22 (0.98–1.52)	0.08
Age, per 1-yr increase	0.99 (0.99–1.01)	0.74
PA:A ratio >1	3.44 (2.78–4.25)	<0.001
All exacerbations during longitudinal follow-up		
Exacerbation in previous yr	2.49 (2.09–2.96)	<0.001
FEV_1, per percentage-point decrease	1.02 (1.01–1.03)	<0.001
SGRQ, per 1-point increase	1.01 (1.01–1.02)	<0.001
GERD	1.75 (1.47–2.08)	<0.001
Age, per 1-yr increase	1.01 (0.99–1.01)	0.83
PA:A ratio >1	1.86 (1.54–2.24)	<0.001

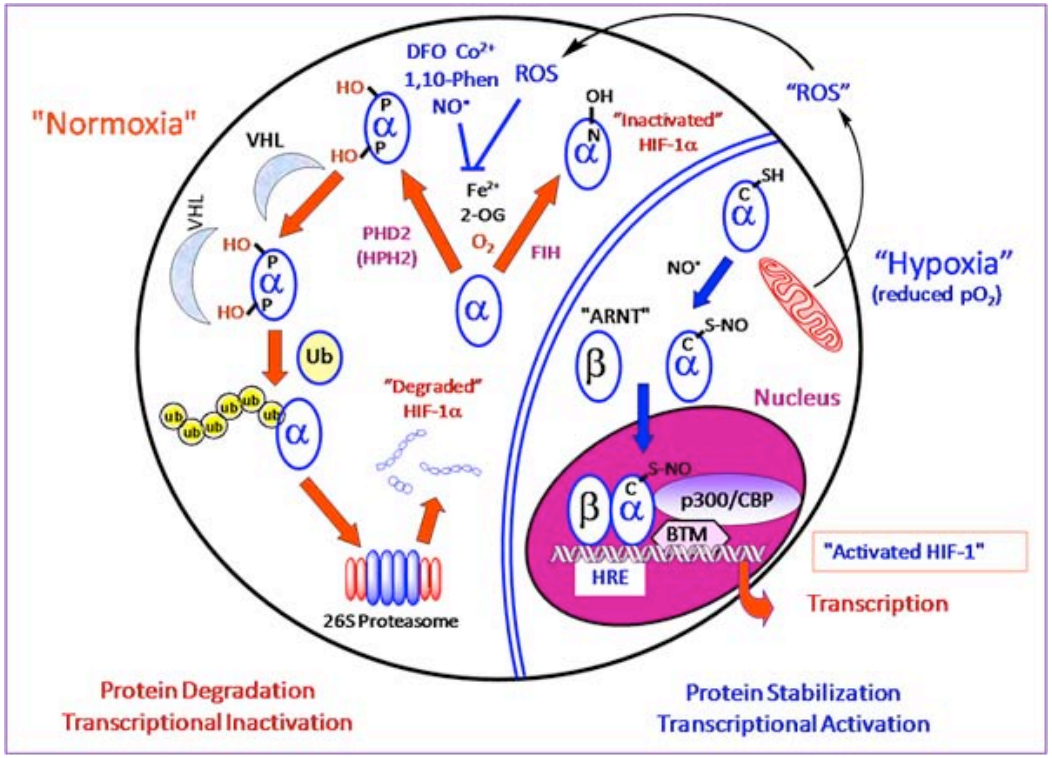
Factor	Year 1	
	Odds Ratio (95% CI)	P Value
Severe exacerbations		
Exacerbation in previous yr	2.43 (1.80–3.29)	<0.001
FEV_1, per percentage-point decrease	1.03 (1.02–1.04)	<0.001
SGRQ, per 1-point increase	1.03 (1.02–1.04)	<0.001
GERD	1.38 (1.01–1.88)	0.41
White-cell count, per $1\times10^3/mm^3$ increase	1.07 (1.01–1.13)	0.01
PA:A ratio >1	2.8 (2.11–3.71)	<0.001
All exacerbations		
Exacerbation in previous yr	3.78 (3.07–4.65)	<0.001
FEV_1, per percentage-point decrease	1.02 (1.01–1.02)	<0.001
SGRQ, per 1-point increase	1.01 (1.00–1.01)	0.002
GERD	1.72 (1.36–2.17)	<0.001
White-cell count, per $1\times10^3/mm^3$ increase	1.05 (0.99–1.09)	0.06
PA:A ratio >1	2.17 (1.71–2.74)	<0.001



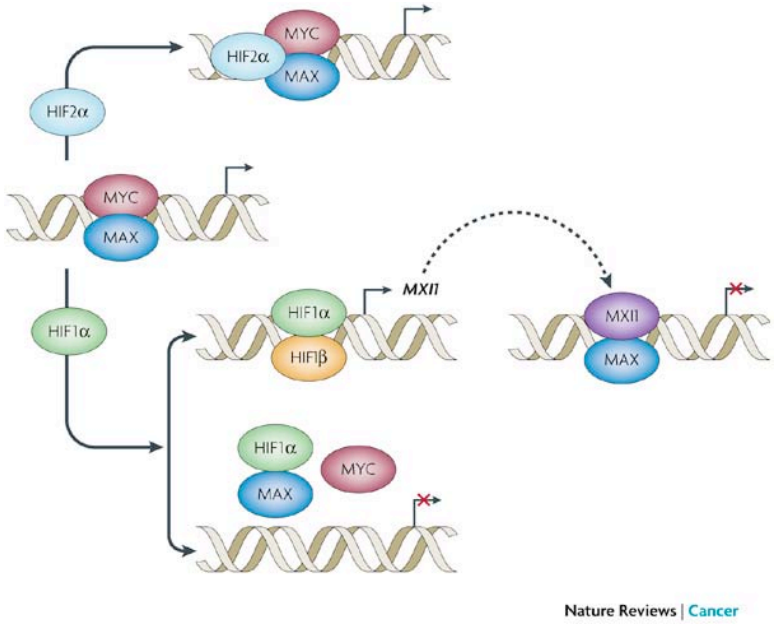
A histogram shows the relationship between the PA:A ratio and the occurrence of severe exacerbations (those requiring hospitalization) at baseline and during follow-up in the COPDGene study.

Multivariate logistic-regression analysis showed a significant association between a PA:A ratio of more than 1 and a history of severe exacerbations at the time of enrollment in the trial. A PA:A ratio of more than 1 was also independently associated with an increased risk of future severe exacerbations . Pulmonary artery enlargement (a PA:A ratio of >1), as detected by CT, was associated with severe exacerbations of COPD.

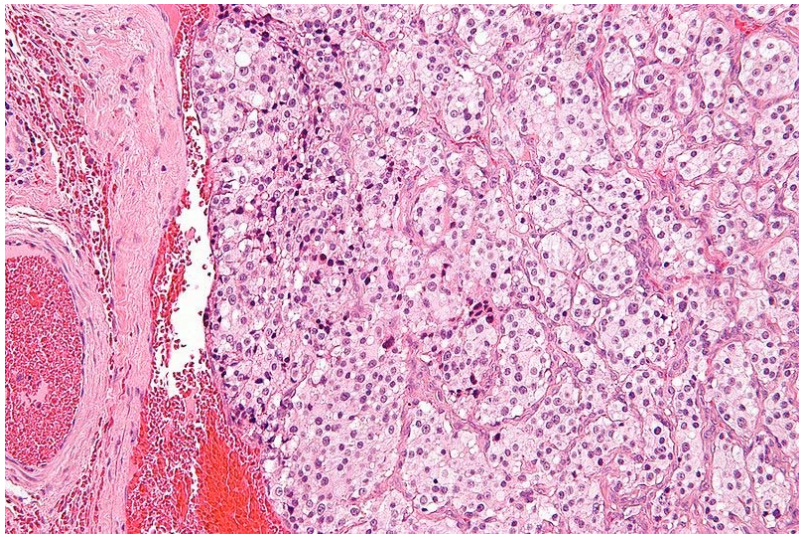
Hypoxie-induzierter Faktor (HIF) ist ein Transkriptionsfaktor, der die Versorgung der Zelle mit Sauerstoff reguliert, indem er eine Balance zwischen Sauerstoffbedarf und Sauerstoffversorgung herstellt. HIF besteht aus einer labilen α-Untereinheit, die in drei Isoformen, HIF-1α, HIF-2α und HIF-3α existiert, und einer β-Untereinheit. Bei normaler Sauerstoffversorgung (Normoxie) ist die α-Untereinheit an zwei spezifischen Prolyl-Resten hydroxyliert. Diese Hydroxylierung führt dazu, dass HIFα über das Hippel-Lindau-Tumor-Suppressor-Protein abgebaut wird. Bei mangelnder Sauerstoffversorgung (Hypoxie) ist die Hydroxylierung von HIF-α gehemmt. Der so stabilisierte Transkriptionsfaktor aktiviert das Erythropoetin-Gen und eine Reihe weiterer Gene, die zur Anpassung der Zelle an eine mangelnde Sauerstoffversorgung erforderlich sind. Weiterhin deuten verschieden Experimente auf HIF induzierte expression von Wachstumsfaktoren der Gruppe Vascular Endothelial Growth Factor (VEGF) hin.

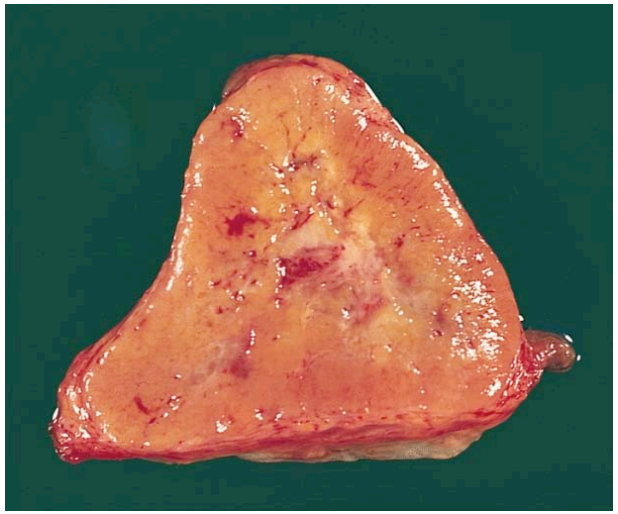


In order to define the role of HIF-1 and HIF-2 in the regulation of hepatic EPO expression, we have generated mice with conditional inactivation of Hif-1α and/or Hif-2α (Epas1) in hepatocytes. We have previously shown that inactivation of the von Hippel–Lindau tumor suppressor pVHL, which targets both HIFs for proteasomal degradation, results in increased hepatic Epo production and polycythemia independent of Hif-1α. Here we show that conditional inactivation of Hif-2α in pVHL-deficient mice suppressed hepatic Epo and the development of polycythemia. Furthermore, we found that physiological Epo expression in infant livers required Hif-2α but not Hif-1α and that the hypoxic induction of liver Epo in anemic adults was Hif-2α dependent. Since other Hif target genes such phosphoglycerate kinase 1 (Pgk) were Hif-1α dependent, we provide genetic evidence that HIF-1 and HIF-2 have distinct roles in the regulation of hypoxia-inducible genes and that EPO is preferentially regulated by HIF-2 in the liver.



A paraganglioma is a rare neuroendocrine neoplasm that may develop at various body sites (including the head, neck, thorax and abdomen). About 97% are benign and cured by surgical removal; the remaining 3% are malignant because they are able to produce distant metastases. "Paraganglioma" is now the most-widely accepted term for these lesions, that have been also described as: glomus tumor, chemodectoma, perithelioma, fibroangioma, and sympathetic nevi. Most paragangliomas are either asymptomatic or present as a painless mass. While all contain neurosecretory granules, only in 1–3% of cases is secretion of hormones such as catecholamines abundant enough to be clinically significant; in that case manifestations often resemble those of phaeochromocytomas. About 75% of paragangliomas are sporadic; the remaining 25% are hereditary (and have an increased likelihood of being multiple and of developing at an earlier age). Mutations of the genes SDHD (previously known as PGL1), PGL2, and SDHC (previously PGL3) have been identified as causing familial head and neck paragangliomas. Mutations of SDHB play an important role in familial adrenal pheochromocytoma and extra-adrenal paraganglioma (of abdomen and thorax), although there is considerable overlap in the types of tumors associated with SDHB and SDHD gene mutations. Paragangliomas may also occur in MEN type 2A and 2B. They are seen in at a higher incidence in people living at high altitude.

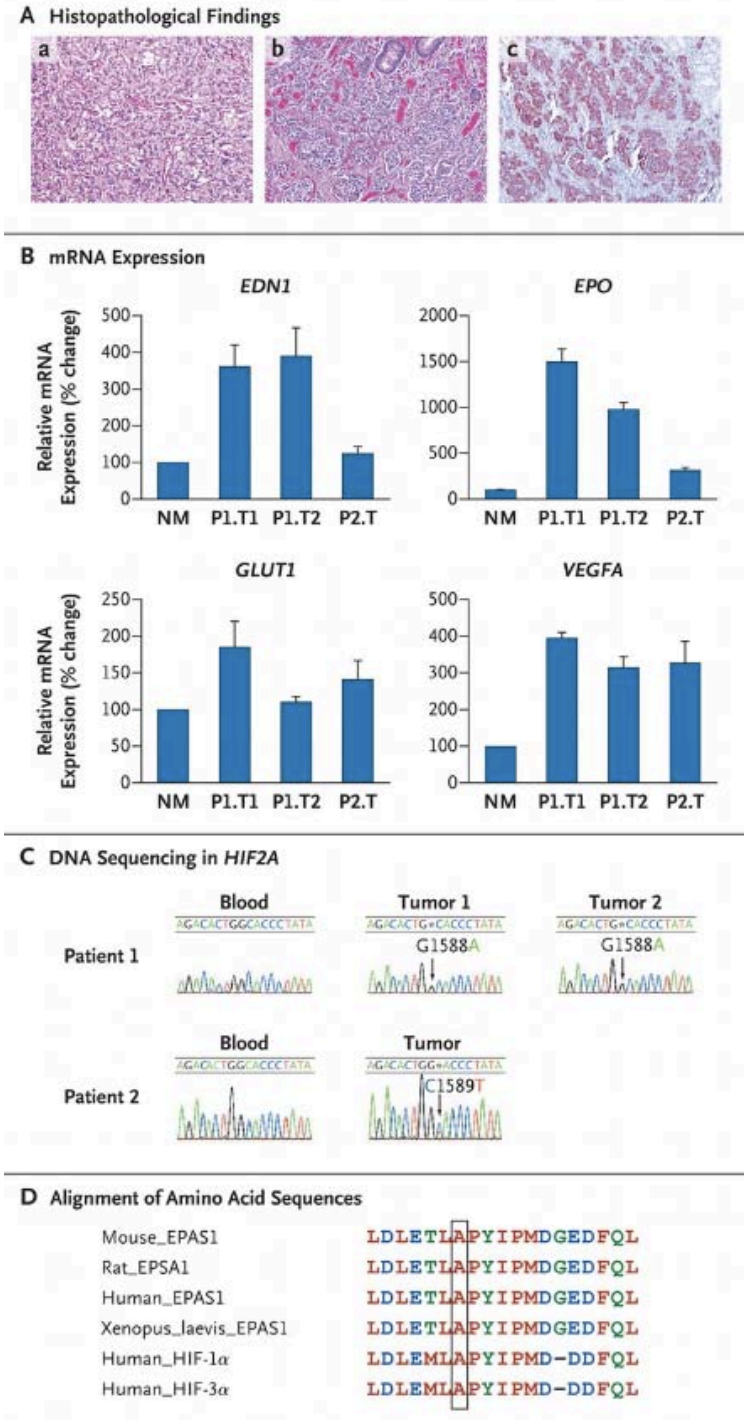


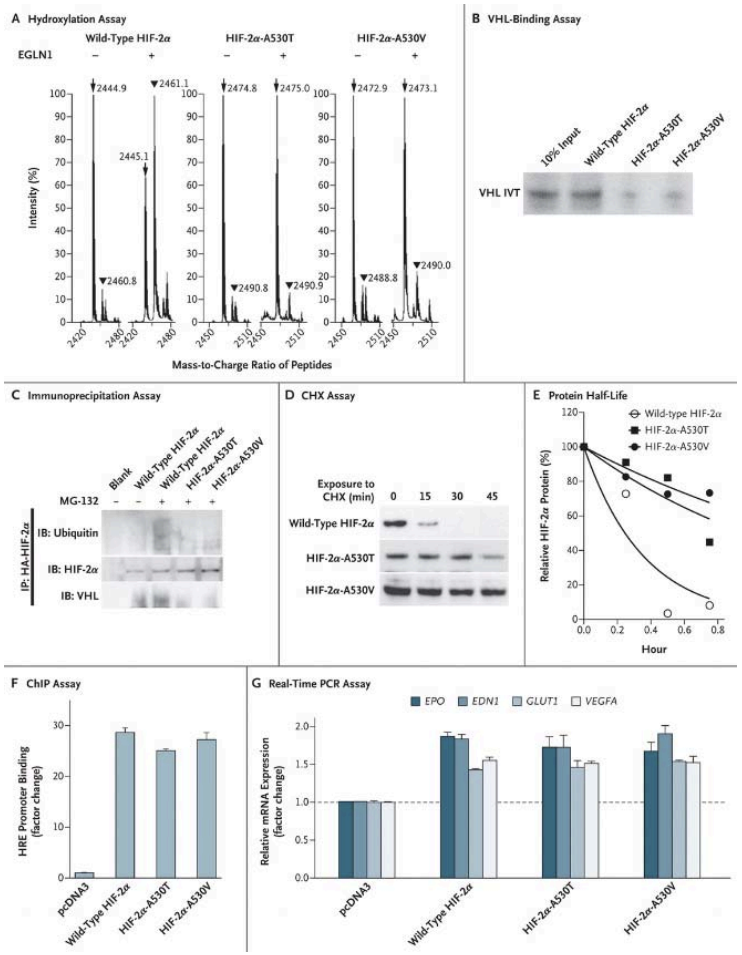


Somatic HIF2A Gain-of-Function Mutations in Paraganglioma with Polycythemia

Hypoxia-inducible factors are transcription factors controlling energy, iron metabolism, erythropoiesis, and development. When these proteins are dysregulated, they contribute to tumorigenesis and cancer progression. However, mutations in genes encoding α subunits of hypoxia-inducible factors (HIF-α) have not previously been identified in any cancer. Here we report two novel somatic gain-of-function mutations in the gene encoding hypoxia-inducible factor 2α (HIF2A) in two patients, one presenting with paraganglioma and the other with paraganglioma and somatostatinoma, both of whom had polycythemia. The two mutations were associated with increased HIF-2α activity and increased protein half-life.

Variable	Patient 1	Patient 2
Age at onset of diagnosed condition		
Polycythemia	At birth	At birth
Multiple paragangliomas	14 yr	18 yr
Multiple somatostatinomas	29 yr	No
Recurrent paragangliomas on imaging	Yes	No
Metastatic tumors on imaging	No	No
Age at onset of clinical characteristics		
Abnormal redness of the body	8 yr	At birth
Blue feet	No	≤1 yr
Red cheeks and lips	8 yr	At birth
Growth or developmental abnormalities	No	No
Marfanoid habitus, gothic palate, arachnodactyly	Yes	No
Cardiac systolic murmur, mild cardiomegaly	Yes	No
Dilatation of ascending aorta	Yes	No
Headache	14 yr	12 yr
Anxiety attacks	No	12 yr
Palpitations	14 yr	No
Blood pressure (mm Hg)		
Before diagnosis of paraganglioma	160/100, 14 yr	210/110, 18 yr
At presentation at NIH	136/95	135/78
Heart rate (bpm)	59	105
Pertinent family history	No	No
Complete blood count and erythropoietin at NIH		
Erythrocytes (per mm³)	7,780,000	7,850,000	5,220,000
Hematocrit (%)	50.5	59.3	44.9
Hemoglobin (g/dl)	14.7	18.8	15.7
Leukocytes (per mm³)	7190	8130	10,040
Platelets (per mm³)	194,000	249,000	367,000
Erythropoietin (mIU/ml)	150	180	36.7
Plasma biochemical test at NIH		
Normetanephrine (pg/ml)	4,834	858	112
Metanephrine (pg/ml)	121	9	61
Norepinephrine (pg/ml)	10,951	1760	498
Epinephrine (pg/ml)	100	7	83
Dopamine (pg/ml)	28	20	46
Chromogranin A (ng/ml)	1640	320	225
Other genes tested: *EPOR, HIF1A, JAK2, PHD, SDHB/C/D, VHL*†	No germline mutations found	No germline mutations found	





We now report somatic gain-of-function HIF2A mutations in paragangliomas and somatostatinomas that were clinically associated with polycythemia. These mutations were identified in the vicinity of the primary hydroxylation site of the HIF-2α protein. The mutations affect prolyl hydroxylation and VHL protein binding, resulting in reduced HIF-2α degradation but intact transcriptional activity and activation of genes downstream of HIF-2. We found increased erythropoietin mRNA and protein levels in both tumors, which may result in a high serum erythropoietin level and polycythemia.

A 69-year-old man presented to the emergency department 2 hours after he awakened with slurred speech. The patient reported a single episode of sharp, self-limited, periumbilical pain after dinner the previous night, and he had awoken that morning with slurred speech, difficulty chewing, blurry vision in both eyes, generalized weakness, and unsteady gait. He had received a diagnosis of hypertension and hyperlipidemia 3 years earlier but had declined pharmacologic treatment. The patient reported no recent trauma or immunizations and no history of similar symptoms. He did not have fevers, night sweats, headaches, nausea, constipation, diarrhea, weight loss, diplopia, leg or arm weakness, or difficulty swallowing. The patient lived at home with four healthy family members. He reported drinking one pint of vodka daily, smoking one pack of cigarettes daily for the past 30 years, and smoking “crack” cocaine three times a week, most recently about 24 hours before presentation. He said that he had never used intravenous drugs and had not been sexually active since his wife died the previous year.

On physical examination, the patient appeared well nourished and in no acute distress. The temperature was 36.2°C (97.2°F), the blood pressure 203/93 mm Hg, the pulse 82 beats per minute, and the respiratory rate 16 breaths per minute.

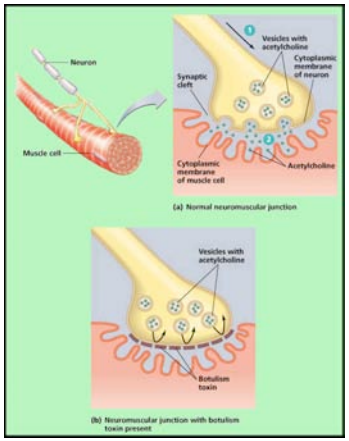
The patient was alert. Speech was decreased in volume, dysarthric, and almost unintelligible. The dysarthria was most pronounced when he was asked to repeat guttural sounds. He could name objects and follow commands. Results of motor, sensory, finger-to-nose, and rapid alternating hand-movement tests were normal. There was bilateral rotary nystagmus. Deep-tendon reflexes were normal. Plantar reflexes were flexor. On cranial-nerve testing, there was weakness on abduction of the right eye. Pupillary responses to light were intact. Gait was not assessed.

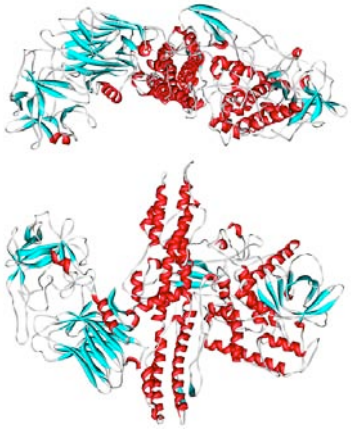
I would empirically administer thiamine with glucose and obtain urgent imaging of the brain, though I cannot identify a single vascular territory to explain this patient's symptoms.

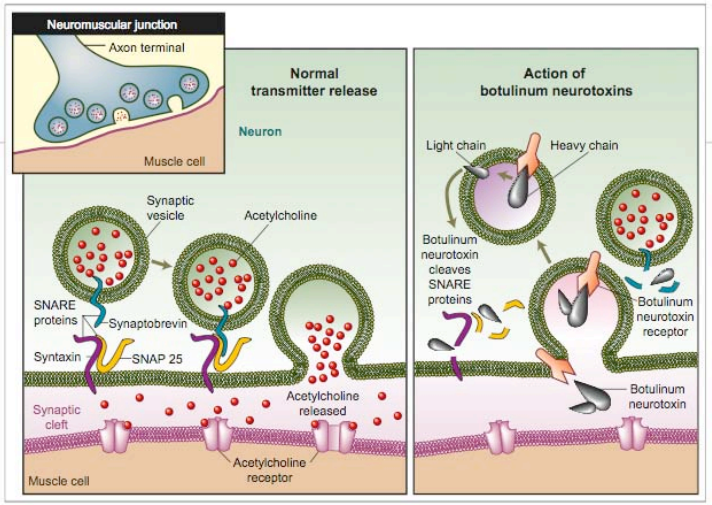
In the early afternoon, before a scheduled MRI and MRA evaluation of the head and neck, the patient was unresponsive, with his eyes closed. He was no longer breathing spontaneously and was intubated. An urgent CT scan of the head showed no acute hemorrhage or infarct. A CT angiogram of the head and neck revealed no evidence of arterial dissection. Results of a lumbar puncture showed a white-cell count of 2 per cubic millimeter with a normal differential count, a glucose level of 53 mg per deciliter (2.9 mmol per liter), and a protein level of 18.2 mg per deciliter, with a negative Gram's stain.

Two possibilities come to the forefront now: myasthenia gravis and botulism. I would order tests for antibodies against the acetylcholine receptor and GQ1b, which are detected in the majority of patients with myasthenia gravis and in those with the Miller Fisher syndrome, respectively.

Botulismus ist eine lebensbedrohliche, meist durch verdorbenes Fleisch oder nicht fachgerecht eingekochtes Gemüse hervorgerufene Vergiftung (auch „Fleischvergiftung“, „Wurstvergiftung“), die von Botulinumtoxin, einem vom Bakterium Clostridium botulinum („botulus“ ist das lateinische Wort für Wurst) produzierten Giftstoff, verursacht wird. In der Lebensmittelherstellung wird das Wachstum des Bakteriums durch Pökeln oder Hitzesterilisation verhindert. Unter anaeroben Bedingungen keimen sie aus und setzen das Gift Botulinumtoxin frei, eines der gefährlichsten Gifte. Streng genommen ist Botulinumtoxin eine Sammelbezeichnung, denn es werden acht Botulinumtoxine unterschieden, die teilweise wirtsspezifisch und unterschiedlich stark giftig sind. Rinder werden vor allem von den Typen C und D betroffen, seltener vom Typ B, der bevorzugt in pflanzlichem Material (fehlgegorenen Silagen) vorkommt. Die Giftwirkung beruht auf der Blockade der Signalübertragung zwischen Nerven und Muskeln. Die Ausschüttung von Acetylcholin wird gehemmt. Zuerst sind meist die Augenmuskeln betroffen, der Patient sieht verschwommen und/ oder doppelt, die Augen fallen immer wieder zu und die Pupillen sind geweitet. Im weiteren Krankheitsverlauf sind Lippen-, Zungen-, Gaumen- und Kehlkopfmuskel betroffen, es kommt zu starker Mundtrockenheit (dadurch Durst), Sprech- und Schluckstörungen. Die betroffene Person hat hierbei typischerweise kein Fieber.



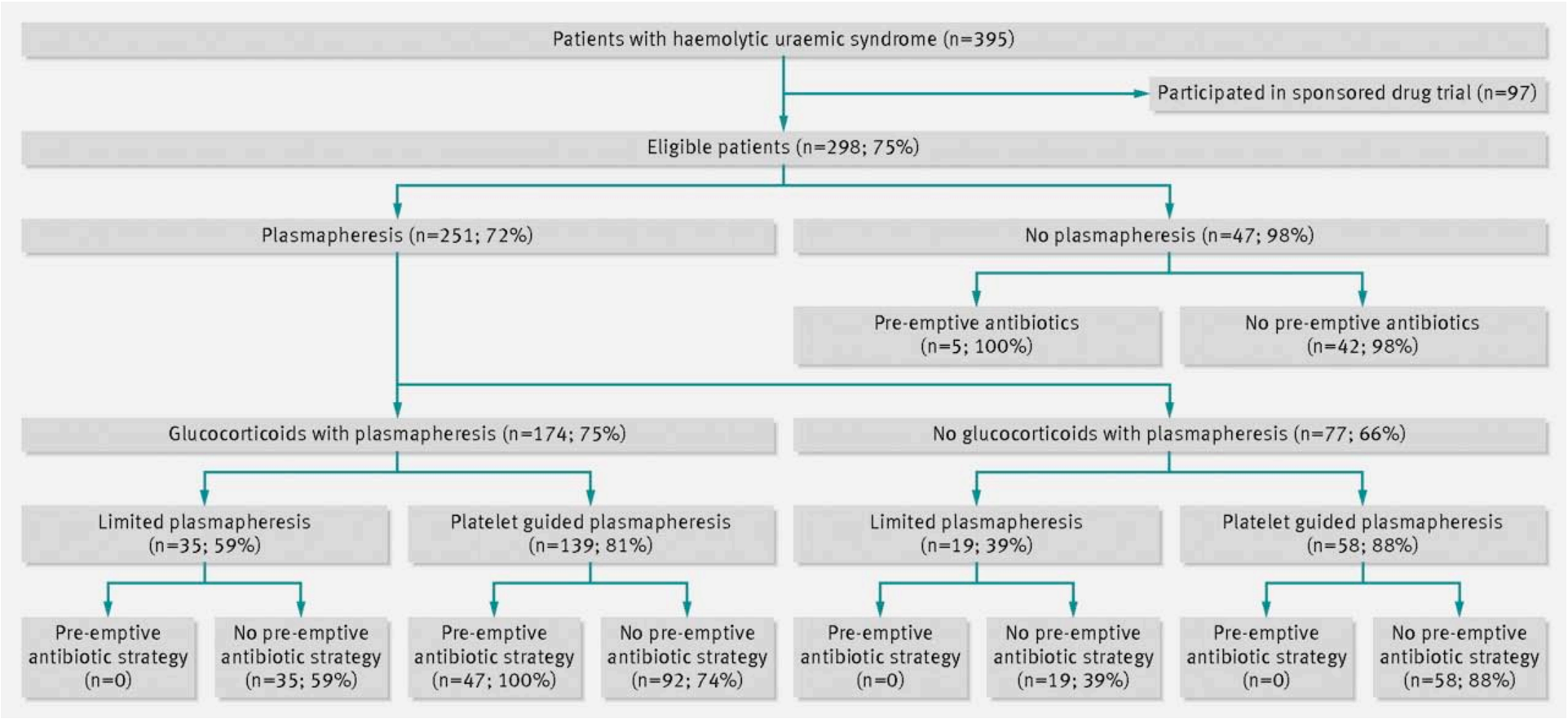




This light chain is an enzyme (a protease) that attacks one of the fusion proteins (SNAP-25, syntaxin or synaptobrevin) at a neuromuscular junction, preventing vesicles from anchoring to the membrane to release acetylcholine.

Validation of treatment strategies for enterohaemorrhagic Escherichia coli O104:H4 induced haemolytic uraemic syndrome: case-control study. (BMJ)

OBJECTIVE: To evaluate the effect of different treatment strategies on enterohaemorrhagic Escherichia coli O104:H4 induced haemolytic uraemic syndrome. DESIGN: Multicentre retrospective case-control study. SETTING: 23 hospitals in northern Germany. PARTICIPANTS: 298 adults with enterohaemorrhagic E coli induced haemolytic uraemic syndrome. MAIN OUTCOME MEASURES: Dialysis, seizures, mechanical ventilation, abdominal surgery owing to perforation of the bowel or bowel necrosis, and death.
RESULTS: 160 of the 298 patients (54%) temporarily required dialysis, with only three needing treatment long term. 37 patients (12%) had seizures, 54 (18%) required mechanical ventilation, and 12 (4%) died. No clear benefit was found from use of plasmapheresis or plasmapheresis with glucocorticoids. 67 of the patients were treated with eculizumab, a monoclonal antibody directed against the complement cascade. No short term benefit was detected that could be attributed to this treatment. 52 patients in one centre that used a strategy of aggressive treatment with combined antibiotics had fewer seizures (2% v 15%, P=0.03), fewer deaths (0% v 5%, p=0.029), required no abdominal surgery, and excreted E coli for a shorter duration.
CONCLUSIONS: Enterohaemorrhagic E coli induced haemolytic uraemic syndrome is a severe self limiting acute condition. Our findings question the benefit of eculizumab and of plasmapheresis with or without glucocorticoids. Patients with established haemolytic uraemic syndrome seemed to benefit from antibiotic treatment and this should be investigated in a controlled trial.



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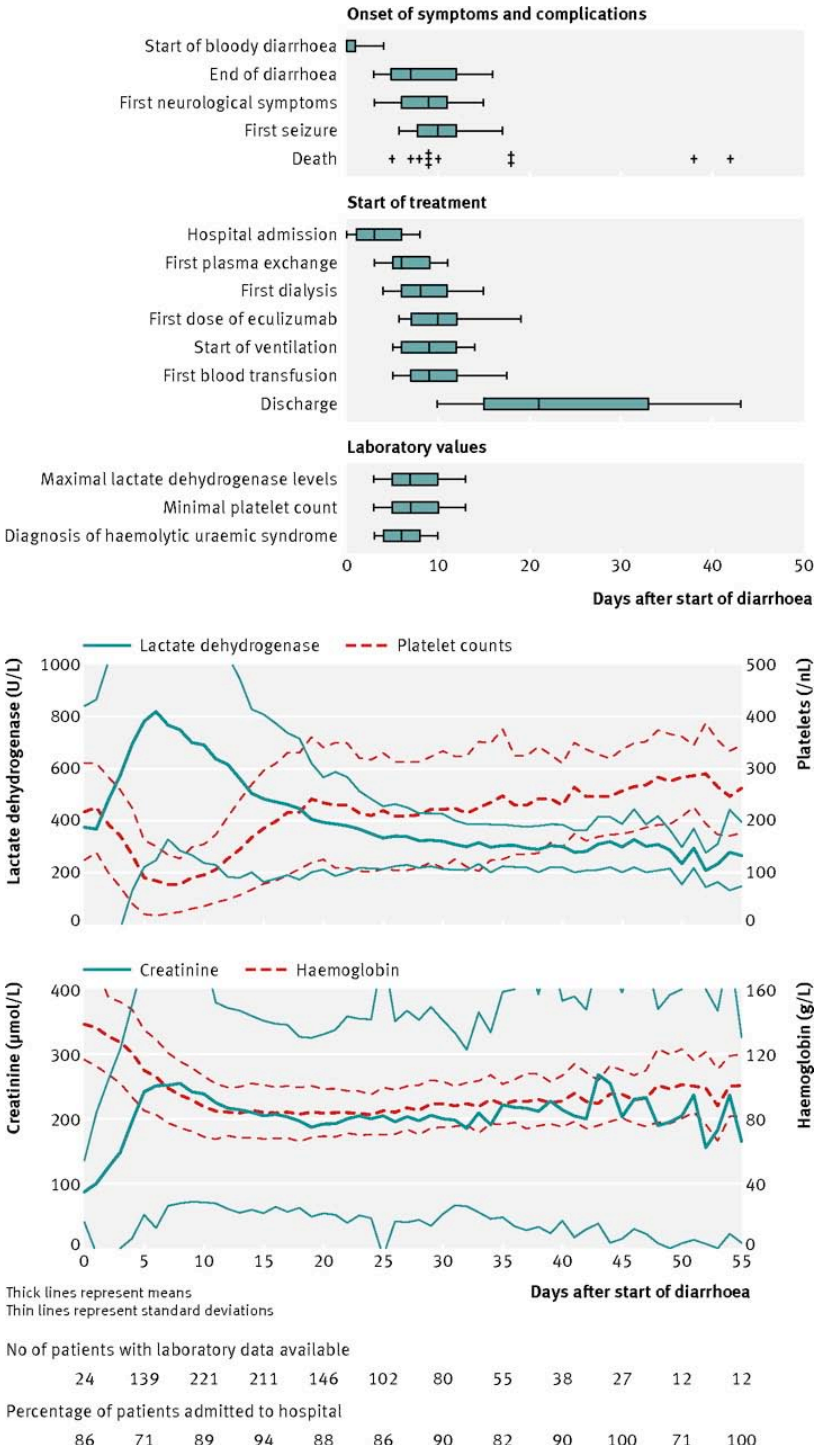
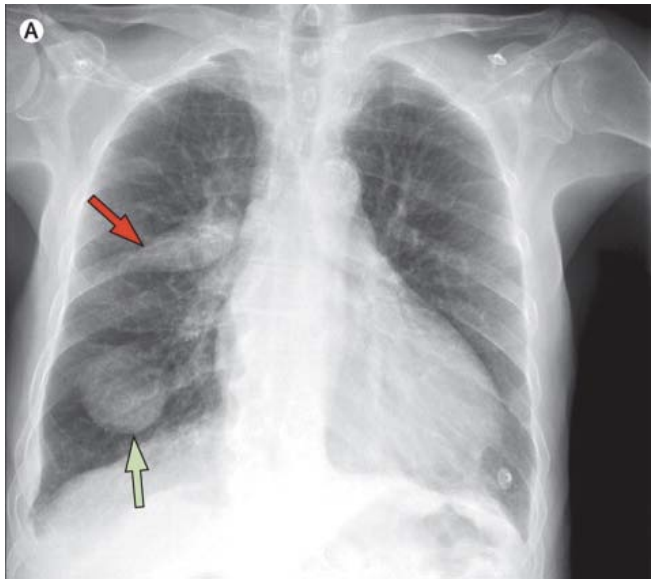


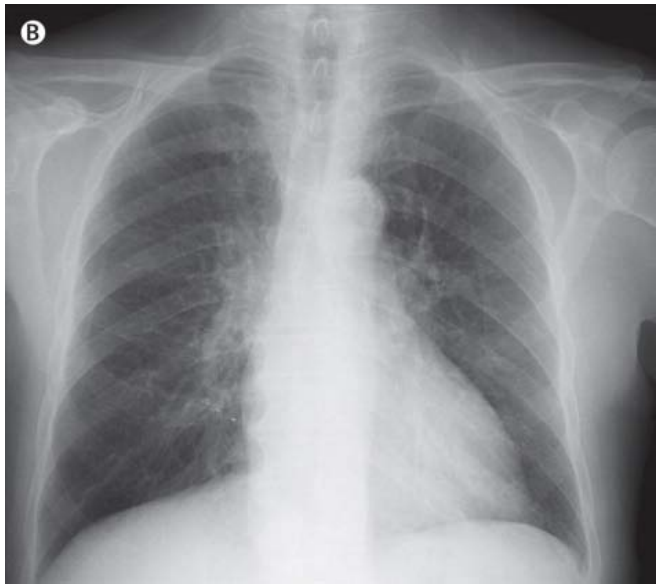
At the beginning of this outbreak the German Society of Nephrology recommended use of plasmapheresis, especially for cases of enterohaemorrhagic E coli associated haemolytic uraemic syndrome with neurological or severe renal involvement. This recommendation is supported by the American Society for Apheresis, which gives a low II-3 recommendation for the usage of plasmapheresis in patients with typical haemolytic uraemic syndrome. It is believed that plasmapheresis might remove the circulating shiga toxin or factors that damage the endothelium.

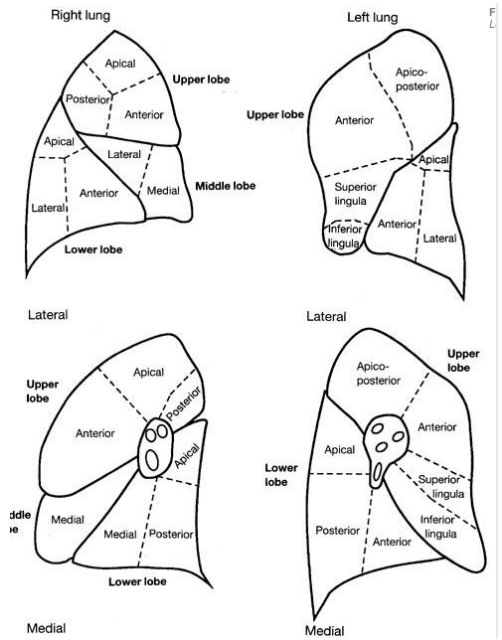
Based on the data presented, patients treated with eculizumab did not improve significantly compared with a control group of patients with the same severity of haemolytic uraemic syndrome. Patients treated with eculizumab still developed new complications, such as seizure or requirement for ventilation, and in more than 40% of the patients plasmapheresis was continued after eculizumab had been started.

Contrary to current belief, antibiotics do not seem to worsen the clinical course in patients with established haemolytic uraemic syndrome, but may be of clinical benefit.

A 79-year-old man presented with an 8 h history of shortness of breath and oedematous legs. He had a history of hypertension, atrial fibrillation, and chronic obstructive pulmonary lung disease.



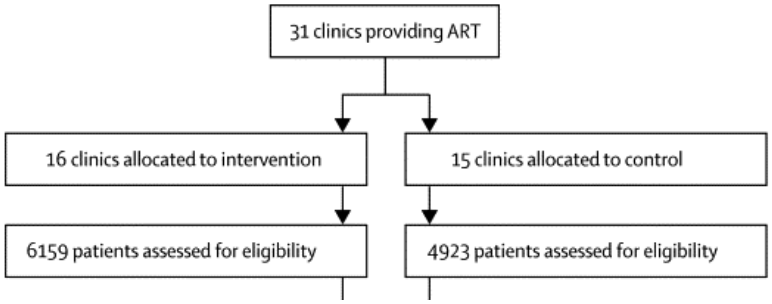


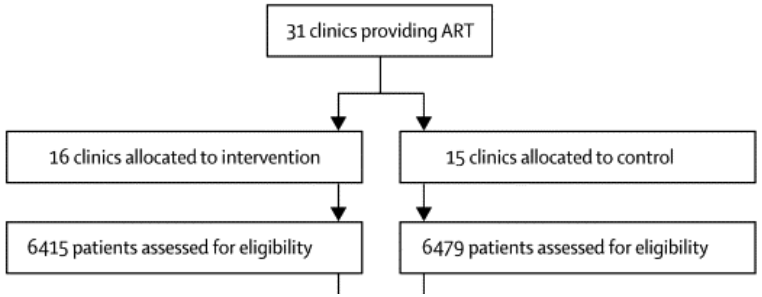


Phantom tumours (or vanishing tumours) of the lung are well known entities in cardiovascular medicine which result from loculation of a pleural effusion within an interlobar fissure from exacerbated congestive heart failure.

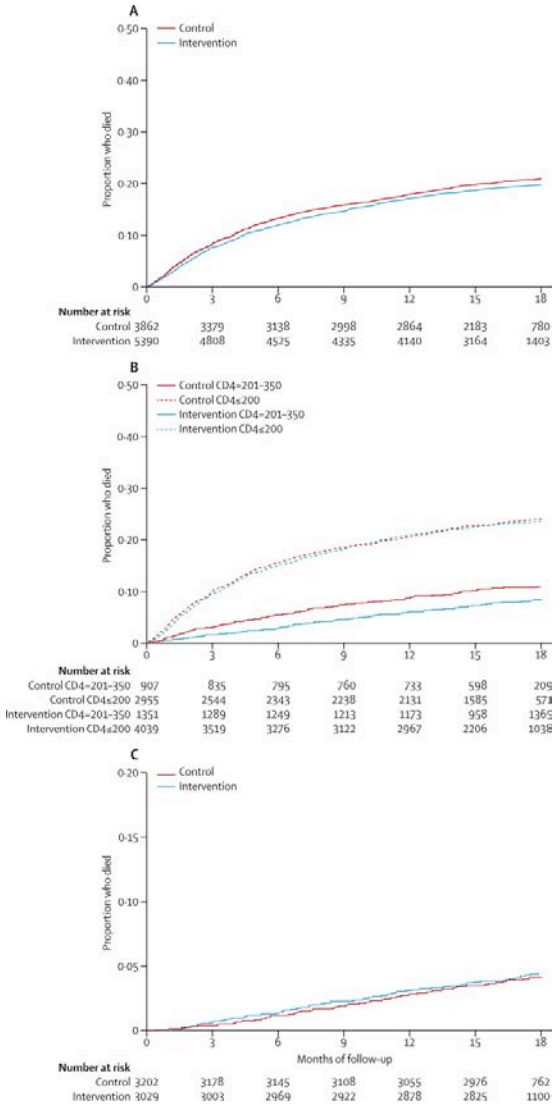
Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial

Robust evidence of the effectiveness of task shifting of antiretroviral therapy (ART) from doctors to other health workers is scarce. We aimed to assess the effects on mortality, viral suppression, and other health outcomes and quality indicators of the Streamlining Tasks and Roles to Expand Treatment and Care for HIV (STRETCH) programme, which provides educational outreach training of nurses to initiate and represcribe ART, and to decentralise care. We undertook a pragmatic, parallel, cluster-randomised trial in South Africa between Jan 28, 2008, and June 30, 2010. We randomly assigned 31 primary-care ART clinics to implement the STRETCH programme (intervention group) or to continue with standard care (control group). The ratio of randomisation depended on how many clinics were in each of nine strata. Two cohorts were enrolled: eligible patients in cohort 1 were adults (aged ≥16 years) with CD4 counts of 350 cells per µL or less who were not receiving ART; those in cohort 2 were adults who had already received ART for at least 6 months and were being treated at enrolment. The primary outcome in cohort 1 was time to death (superiority analysis). The primary outcome in cohort 2 was the proportion with undetectable viral loads (<400 copies per mL) 12 months after enrolment (equivalence analysis, prespecified difference <6%). Patients and clinicians could not be masked to group assignment. The interim analysis was blind, but data analysts were not masked after the database was locked for final analysis. Analyses were done by intention to treat.





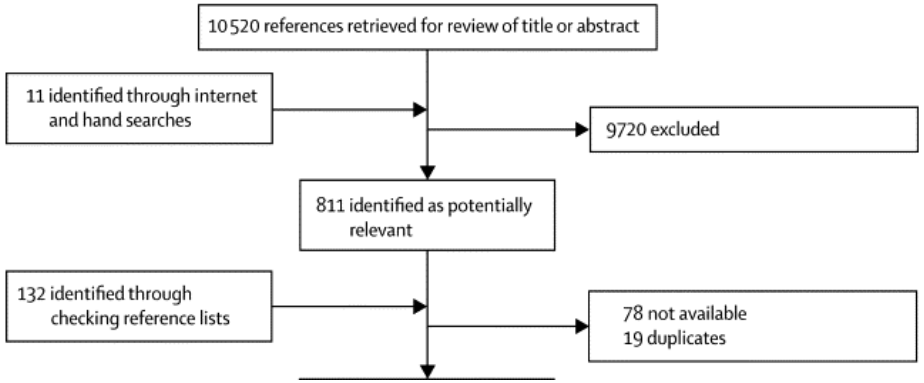
	Intervention group	Control group
Cohort 1		
Number of patients	5390	3862
Women	3604 (67%)	2681 (69%)
Age (years)	36 (30–43)	35 (29–42)
National identity number recorded	4767 (88%)	3184 (82%)
CD4 (cells per μL)	141 (70–201)	137 (70–197)
0–49	934 (17%)	678 (18%)
50–99	949 (18%)	720 (19%)
100–199	2141 (40%)	1547 (40%)
200–350	1366 (25%)	917 (24%)
WHO stage recorded*	3057 (57%)	1719 (45%)
Stage I	1582/3057 (52%)	551/1719 (32%)
Stage II	637/3057 (21%)	470/1719 (27%)
Stage III	725/3057 (24%)	653/1719 (38%)
Stage IV	113/3057 (4%)	45/1719 (3%)
Weight recorded	4400 (82%)	2875 (74%)
Weight (kg)	59 (14)	58 (14)
Present tuberculosis	301 (6%)	200 (5%)
Admitted in the year before enrolment	392 (7%)	313 (8%)
Cohort 2		
Number of patients	3029	3202
Women	2113 (70%)	2332 (73%)
Age (years)	38 (32–44)	38 (32–45)
National identity number recorded	2859 (94%)	2958 (92%)
Duration on ART (months)	13·9 (6·8–21·7)	13·7 (7·3–22·3)
ART regimen		
First line (stavudine, lamivudine, efavirenz)	1846 (61%)	2056 (64%)
First line (stavudine, lamivudine, nevirapine)	1012 (33%)	1011 (32%)
Second line (zidovudine, didanosine, lopinavir)	37 (1%)	28 (1%)
Other	109 (4%)	100 (3%)
Not known	25 (1%)	7 (<1%)
Viral load <400 copies per mL	2378 (79%)	2507 (78%)
Weight recorded	2886 (95%)	3128 (98%)
Weight (kg)	61 (13)	62 (13)
Present tuberculosis	241 (8%)	186 (6%)
Admitted in the year before enrolment	282 (9%)	299 (9%)



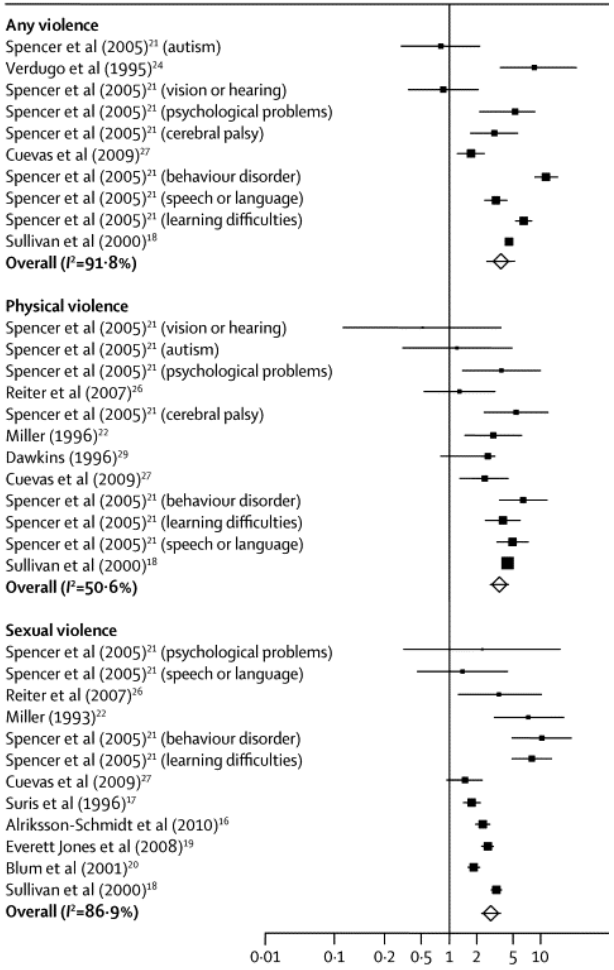
We have shown that task shifting of the primary responsibility for ART from doctors to primary-care nurses in a large-scale public sector programme did not improve survival of patients not yet taking ART with CD4 counts of 350 cells per μL or less, but did in patients with CD4 counts of 201—350 cells per μL, although the difference was not significant. It did achieve its second primary goal of equivalent viral load suppression in patients already taking ART at enrolment.

Prevalence and risk of violence against children with disabilities: a systematic review and meta-analysis of observational studies

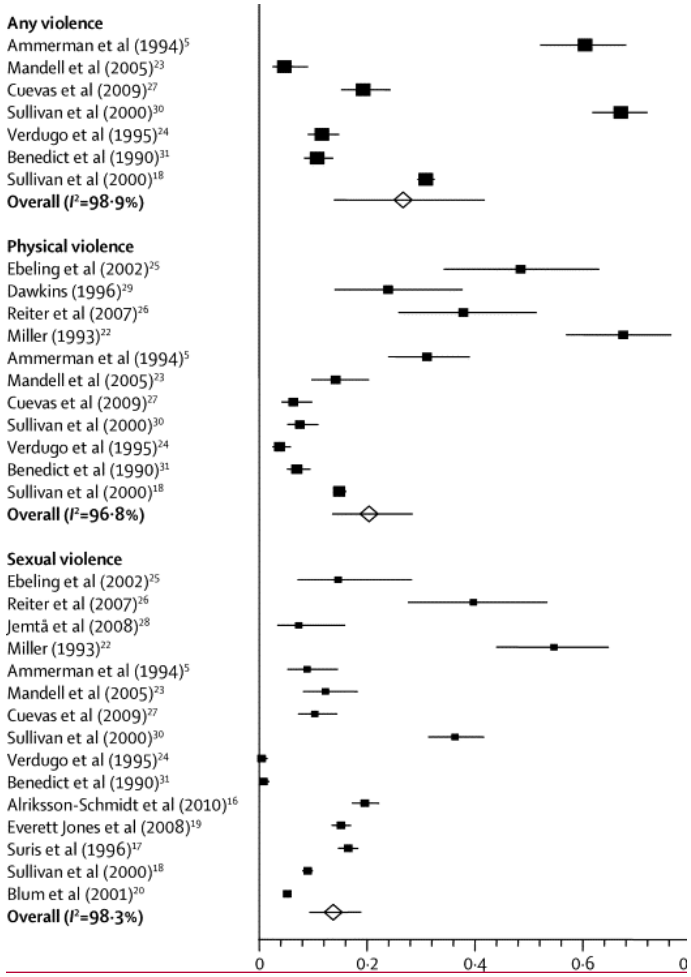
Globally, at least 93 million children have moderate or severe disability. Children with disabilities are thought to have a substantially greater risk of being victims of violence than are their non-disabled peers. Establishment of reliable estimates of the scale of the problem is an essential first step in the development of effective prevention programmes. We therefore undertook a systematic review and meta-analysis to synthesise evidence for the prevalence and risk of violence against children with disabilities. For this systematic review and meta-analysis, we searched 12 electronic databases to identify cross-sectional, case-control, or cohort studies reported between Jan 1, 1990, and Aug 17, 2010, with estimates of prevalence of violence against children (aged ≤18 years) with disabilities or their risk of being victims of violence compared with children without disabilities.



	Study design	All studies						Prevalence only		Risk only				Quality score	
		Sample	Bias	Sample size	Violence measure	Disability measure	Refusers described	Prevalence with CI	Subjects described	Confounders controlled	Odds ratio with CI	Suitable control	Subjects described	Prevalence*	Risk†
Prevalence and risk															
Alriksson-Schmidt et al (2010)[35]	CS	1	1	1	1	0	0	0	0	1	1	1	0	4	7
Blum et al (2001)[29]	CS	1	1	1	1	0	0	0	1	0	0	1	1	5	6
Cuevas et al (2009)[37]	CS	1	0	1	1	1	0	0	1	1	1	1	1	5	8
Dawkins (1996)[30]	CS	1	0	1	1	1	0	0	0	0	0	1	0	4	5
Everett Jones et al (2008)[33]	CS	1	1	1	1	0	0	1	1	1	1	1	0	6	7
Miller (1993)[23]	CS	1	1	1	1	1	0	0	1	0	0	1	1	6	7
Reiter et al (2007)[25]	CS	0	1	1	1	1	0	0	1	0	0	1	1	5	6
Sullivan et al (2000)[28]	CS	1	1	1	1	1	1	0	0	0	0	1	0	6	7
Suris et al (1996)[17]	CS	1	1	1	1	0	0	0	1	0	0	1	1	5	6
Verdugo et al (1995)[24]	CS	0	1	1	1	0	0	0	0	0	0	1	1	3	5
Prevalence only															
Ammerman et al (1994)[6]	CS	0	1	1	1	1	0	0	1	..	..	..	..	5	..
Benedict et al (1990)[31]	Cohort	1	1	1	1	1	1	0	1	..	..	..	..	7	..
Ebeling et al (2002)[36]	CS	0	0	0	0	1	1	0	1	..	..	..	..	3	..
Jemtå et al (2008)[18]	CS	1	1	1	1	1	0	0	1	..	..	..	..	6	..
Mandell et al (2005)[27]	CS	1	1	1	0	1	0	0	1	..	..	..	..	5	..
Sullivan et al (2000)[26]	CS	1	1	1	1	1	1	0	1	..	..	..	..	7	..
Risk only															
Spencer et al (2005)[32]	Cohort	1	1	1	1	1	1	..	..	1	1	1	0	..	9



Prevalence of violence in children with disabilities according to type of violence



Risk estimates of violence in children with disabilities according to type of violence

The results of our review show that although awareness of the risks of violence against children with disabilities has increased, robust evidence continues to be scarce because of a lack of well designed research studies, poor measurement of disability and violence, and insufficient assessment in studies of whether violence preceded the development of disabilities.

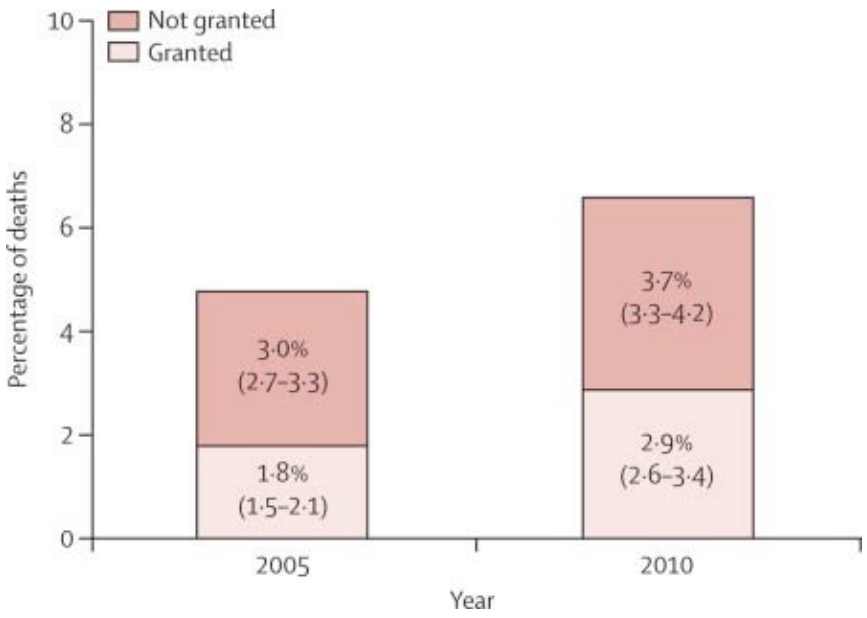
Trends in end-of-life practices before and after the enactment of the euthanasia law in the Netherlands from 1990 to 2010: a repeated cross-sectional survey

In 2002, the euthanasia act came into effect in the Netherlands, which was followed by a slight decrease in the euthanasia frequency. We assessed frequency and characteristics of euthanasia, physician-assisted suicide, and other end-of-life practices in 2010, and assessed trends since 1990. In 1990, 1995, 2001, 2005, and 2010 we did nationwide studies of a stratified sample from the death registry of Statistics Netherlands, to which all deaths and causes were reported. We mailed questionnaires to physicians attending these deaths (2010: n=8496 deaths). All cases were weighted to adjust for the stratification procedure and for differences in response rates in relation to the age, sex, marital status, region of residence, and cause and place of death.
In 2010, of all deaths in the Netherlands, 2·8% were the result of euthanasia. This rate is higher than the 1·7% in 2005, but comparable with those in 2001 and 1995. Since 2002, the Netherlands has been one of the few countries where euthanasia and physician-assisted suicide are, under strict conditions, regulated by law. Comparable laws exist in Belgium and Luxembourg; Oregon, Montana, Washington (USA), and Switzerland have legally regulated assistance in suicide. In the Netherlands, euthanasia is defined as the administering of lethal drugs by a physician with the explicit intention to end a patient's life on the patient's explicit request. In physician-assisted suicide the patient self-administers medication that was prescribed intentionally by a physician.

	1990	1995	2001	2005	2010
Number of deaths in the Netherlands	128 824	135 675	140 377	136 402	136 056
Number of studied cases	5197	5146	5617	9965	6861
Most important end-of-life decision					
Euthanasia	141 (1·7% [1·4–2·1])	257 (2·4% [2·1–2·6])	310 (2·6% [2·3–2·8])	294 (1·7% [1·5–1·8])	475 (2·8% [2·5–3·2])
Assisted suicide	18 (0·2% [0·1–0·3])	25 (0·2% [0·1–0·3])	25 (0·2% [0·1–0·3])	17 (0·1% [<0·1–0·1])	21 (0·1% [0·1–0·2])
Ending of life without explicit patient request	45 (0·8% [0·6–1·1])	64 (0·7% [0·5–0·9])	42 (0·7% [0·5–0·9])	24 (0·4% [0·2–0·6])	13 (0·2% [0·1–0·3])
Intensified alleviation of symptoms	1166 (18·8% [17·9–19·9])	1161 (19·1% [18·1–20·1])	1312 (20·1% [19·1–21·1])	1478 (24·7% [23·5–26·0])	2202 (36·4% [35·2–37·6])
Forgoing of life-prolonging treatment	991 (17·9% [17·0–18·9])	1097 (20·2% [19·1–21·3])	1210 (20·2% [19·1–21·3])	767 (15·6% [15·0–16·2])	974 (18·2% [17·3–19·1])
Total	2361 (39·4% [38·1–40·7])	2604 (42·6% [41·3–43·9])	2899 (43·8% [42·6–45·0])	2570 (42·5% [41·1–43·9])	3685 (57·8% [56·7–59·0])
Continuous deep sedation*†	NA	NA	..	521 (8·2% [7·8–8·6])	789 (12·3% [11·6–13·1])
Patient deciding to end life by stopping eating and drinking	NA	NA	NA	NA	18 (0·4% [0·3–0·6])

	All deaths in 2010 (%)
Age (years)	
0–64 (n=2079)	19%
65–79 (n=2156)	31%
≥80 (n=2626)	51%
Sex	
Male (n=3538)	49%
Female (n=3278)	52%
Cause of death	
Cancer (n=3055)	31%
Cardiovascular disease (n=931)	22%
Other or unknown (n=2875)	47%
Type of physician*	
General practitioner (n=3424)	45%
Clinical specialist (n=1248)	26%
Elderly care physician (n=1588)	29%
Total (n=6861)	100%

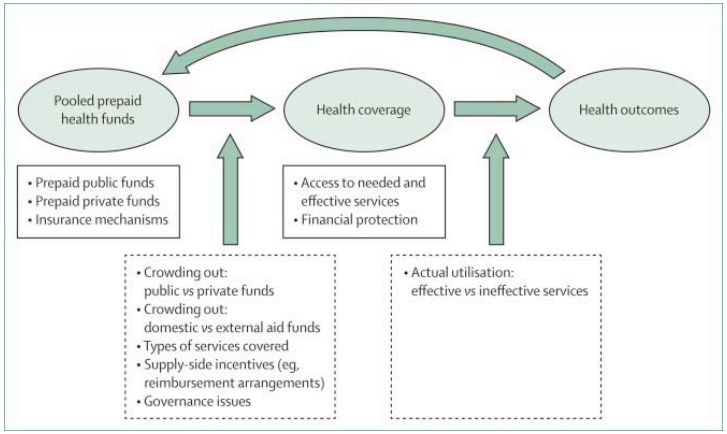
Weighted percentage (95% CI) of all deaths preceded by a granted or ungranted request for euthanasia or physician-assisted suicide
A request can be ungranted for different reasons, among which a refusal of the physician, or the patient dying before the physician could decide on granting the request. There were 9965 deaths in 2005 and 6861 deaths in 2010. Absolute unweighted numbers: 252 granted requests and 251 ungranted for euthanasia in 2005; and 496 granted requests and 270 ungranted requests in 2010.



In conclusion, 8 years after the enactment of the Dutch euthanasia law, the incidence of euthanasia and physician-assisted suicide is comparable with that in the period before the law.

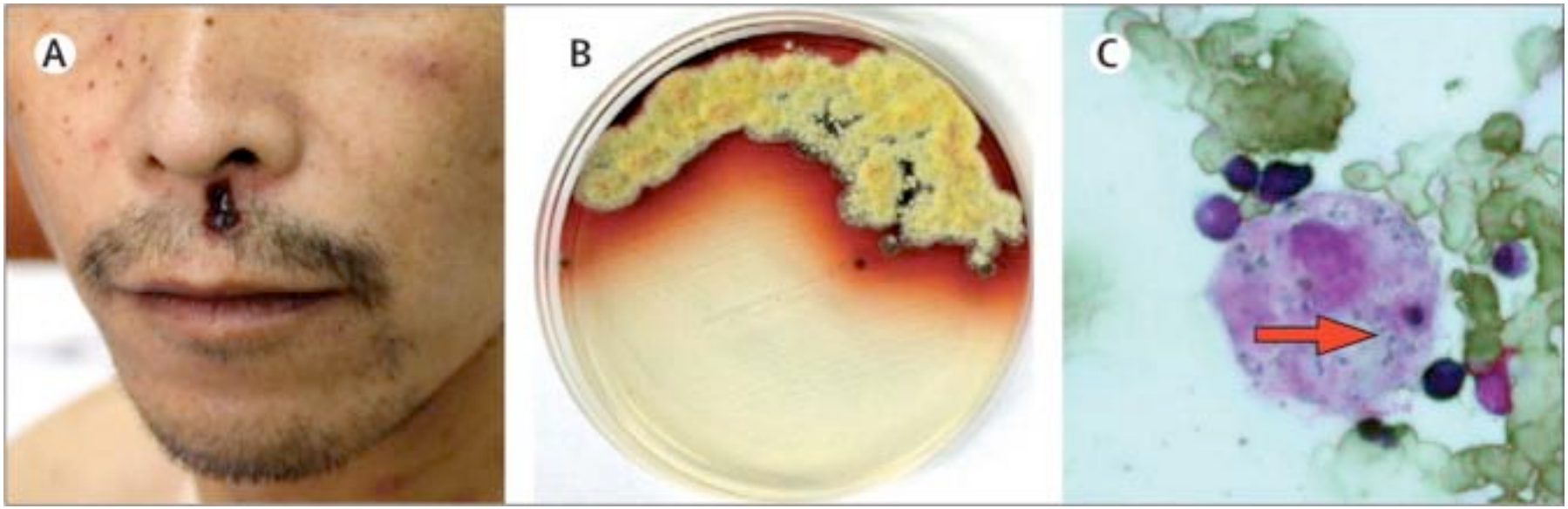
Does progress towards universal health coverage improve population health?

Many commentators, including WHO, have advocated progress towards universal health coverage on the grounds that it leads to improvements in population health. In this report we review the most robust cross-country empirical evidence on the links between expansions in coverage and population health outcomes, with a focus on the health effects of extended risk pooling and prepayment as key indicators of progress towards universal coverage across health systems. The evidence suggests that broader health coverage generally leads to better access to necessary care and improved population health, particularly for poor people. However, the available evidence base is limited by data and methodological constraints, and further research is needed to understand better the ways in which the effectiveness of extended health coverage can be maximised, including the effects of factors such as the quality of institutions and governance.



Notwithstanding these many caveats, there is a growing amount of work supporting the view that a country's progress towards universal coverage leads to better health, especially for poor people. However, success depends crucially on the details of implementation, such as good governance, maintenance of quality standards, careful choice of benefits package, and targeting populations who are especially vulnerable.

A 38-year-old man presented to his local doctor in Qingyuan, Guangdong Province, China, with generalised fatigue. He had had fever for 2 weeks, a non-productive cough, and a 5 kg weight loss. He was treated with antibiotics for 3 days, but the fever continued. He fainted twice at work, falling to the ground. He was taken to the local hospital by his coworkers. Because he admitted to having had unprotected sex with commercial sex workers, an HIV test was done.



Penicilliosis is a subtropical infection caused by the dimorphic fungus, Penicillium marneffei, and occurs in southeast Asia and southern China. Penicilliosis is the sixth most common cause of death in HIV patients in southern China, a region with many immigrants from other provinces and neighbouring countries