What is new in Haemolytic Uraemic Syndrome?

Dr Sally Johnson

Consultant Paediatric Nephrologist, Great North Children's Hospital

and National Renal Complement Therapeutics Centre

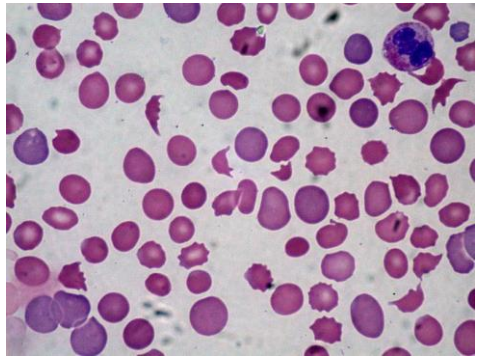
Nephrology for General Paediatricians – Manchester 15th June 2018

Overview

- What is HUS?
- Terminology
- Shiga-toxin producing E.coli
- A little bit about atypical HUS
  - National aHUS Service
- The ECUSTEC trial
- Key take home messages

What is HUS?

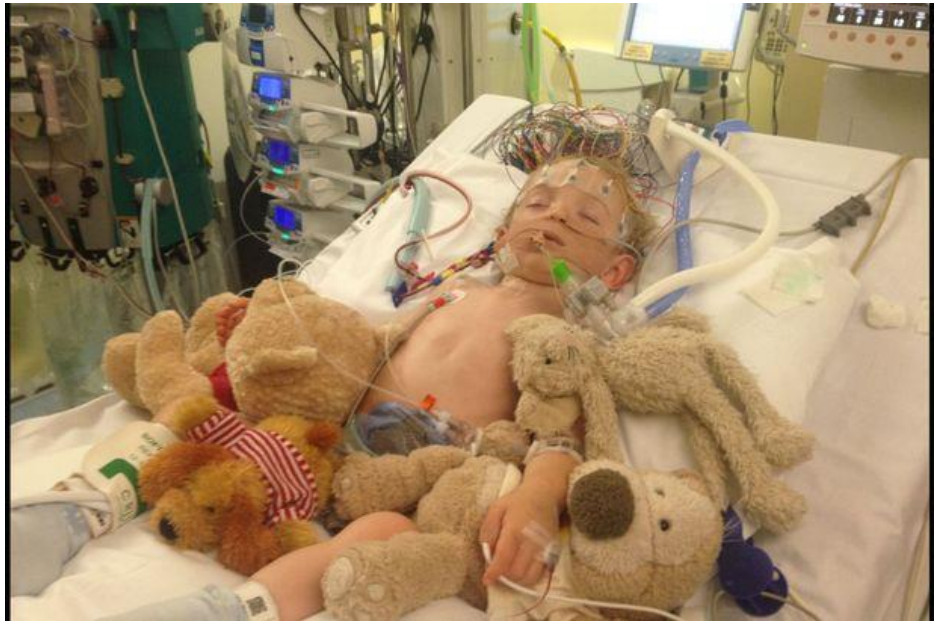
NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE



- Classic triad
  - Microangiopathic haemolytic anaemia (film, LDH)
  - Thrombocytopenia
  - Acute kidney injury
- 100-120 paediatric cases per year in UK
- 90% follow infection with shiga-toxin producing E.coli (STEC or VTEC)
- 10% “Atypical HUS”

Clinical course of HUS

- Management is entirely supportive
  - 50% require renal replacement therapy (mean 10 days)
  - Red cell transfusion
  - Nutrition
  - Folic acid supplementation
  - PICU often required
- 1-3% acute mortality
- Extra renal complications
  - 20-25% central nervous system
  - Severe colitis
  - Pancreatitis
- Outcome
  - 12% End stage renal disease or death
  - 25% Chronic kidney disease



Terminology for HUS keeps changing

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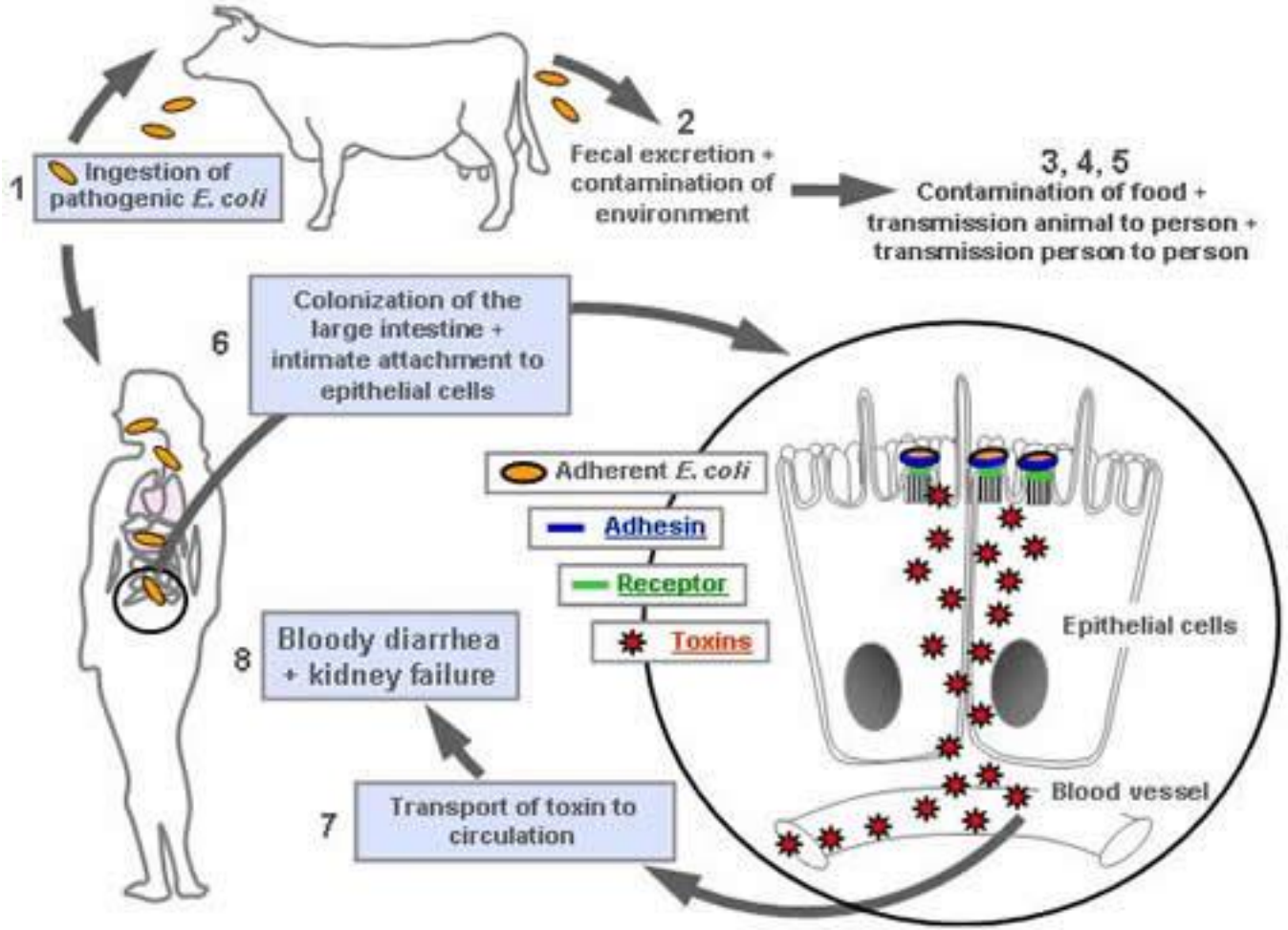
- Diarrhoea positive or diarrhoea negative
- D+ or D-
- Typical or atypical
- **STEC or atypical**

STEC pathogenesis



http://www.ecl-lab.ca/en/ecoli/pathogenesis.asp

Prevalence of STEC in UK cattle

- Herd-level prevalence rate (mean, 95% CI)
  - 0·236 (0·166–0·325) Scotland
  - 0·213 (0·156–0·283) England and Wales
- Pat-level prevalence rate (mean, 95% CI)
  - 0·106 (0·067–0·163) Scotland
  - 0·069 (0·044–0·107) England and Wales
- “Super-shedders”

Henry Epidemiol Infect 2017

STEC epidemiology

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Public Health England

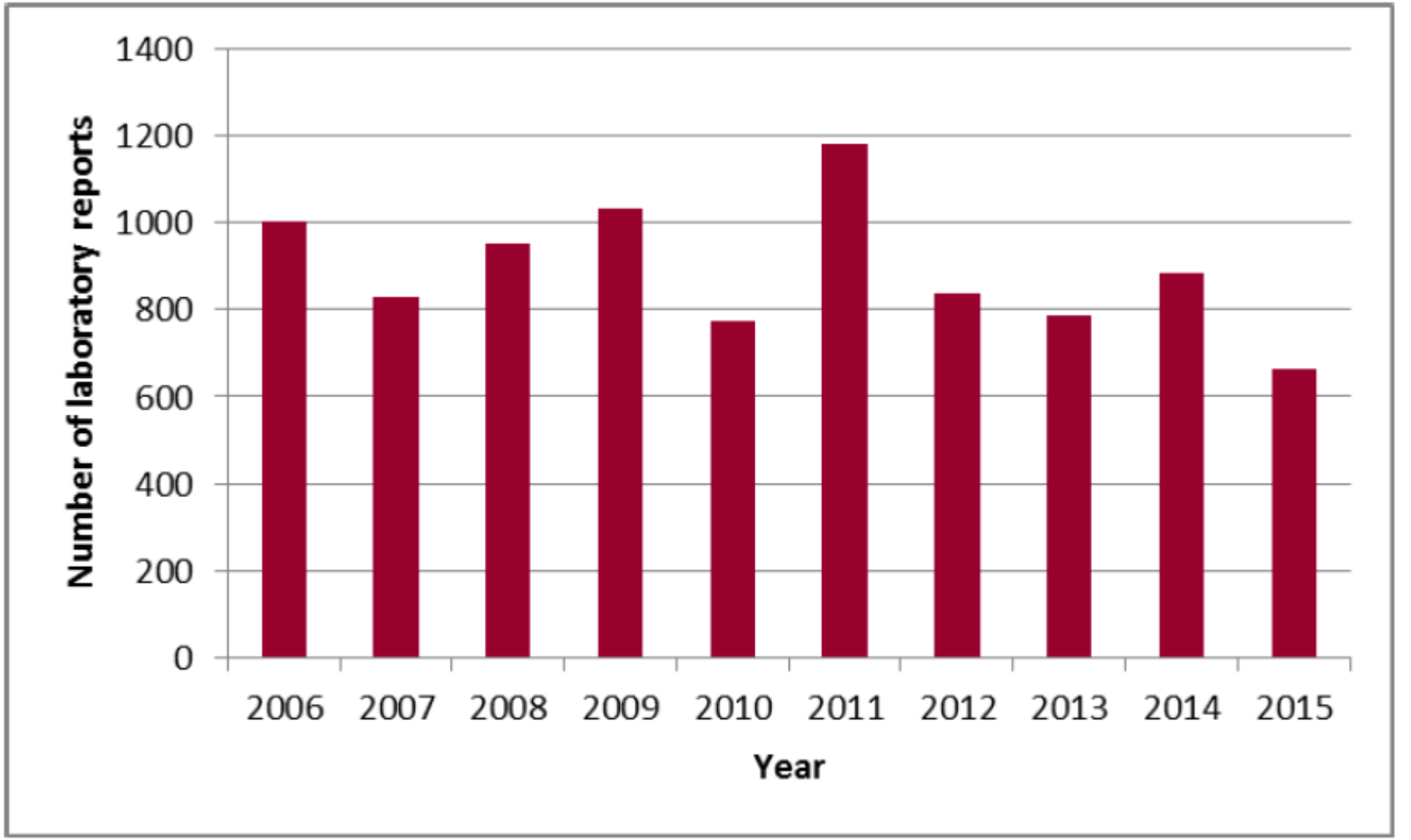
Protecting and improving the nation's health

Vero cytotoxin-producing *Escherichia coli* (VTEC) O157 data 2006 to 2015

November 2016

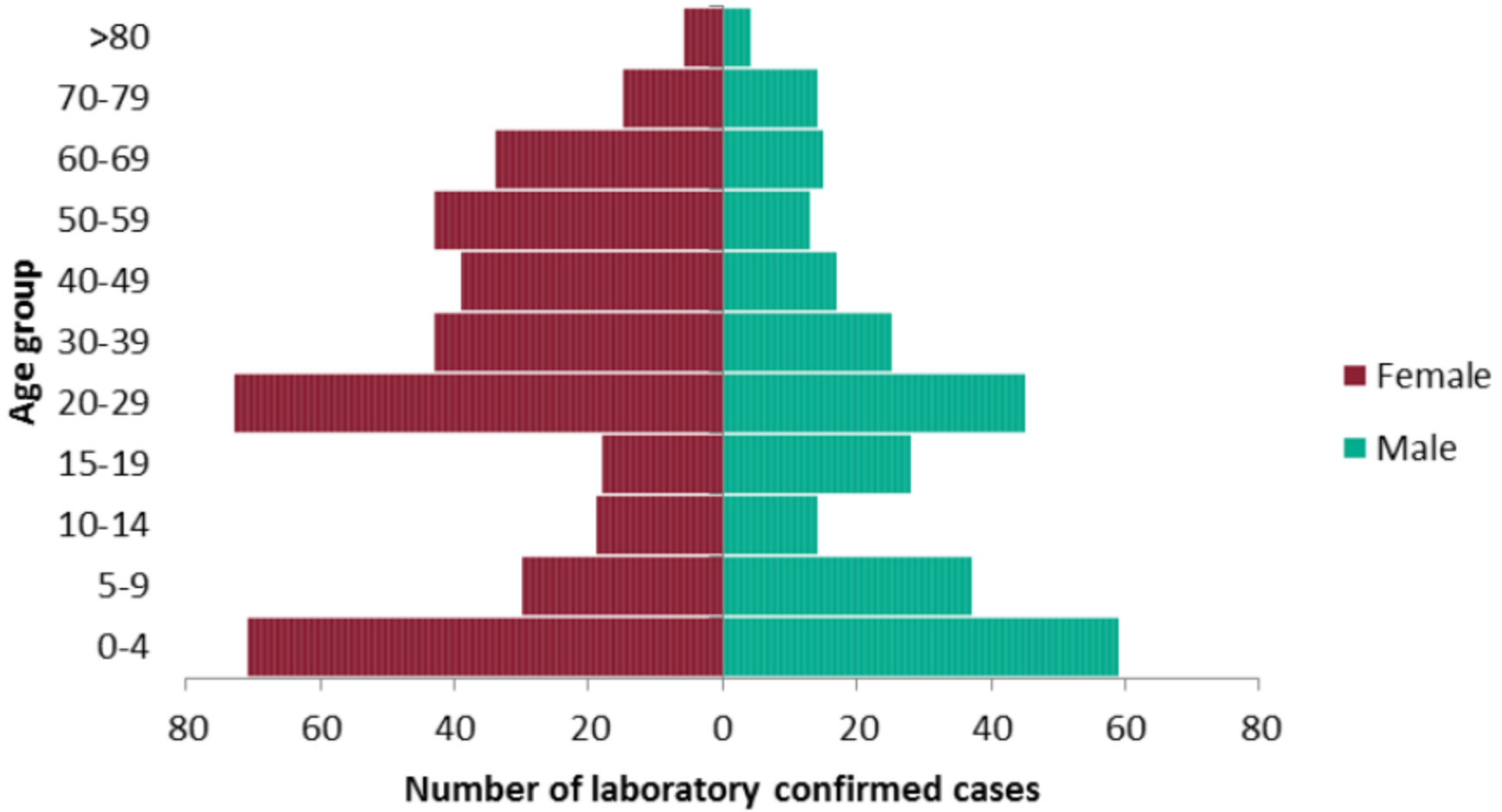
National laboratory data for residents of England and Wales

STEC epidemiology

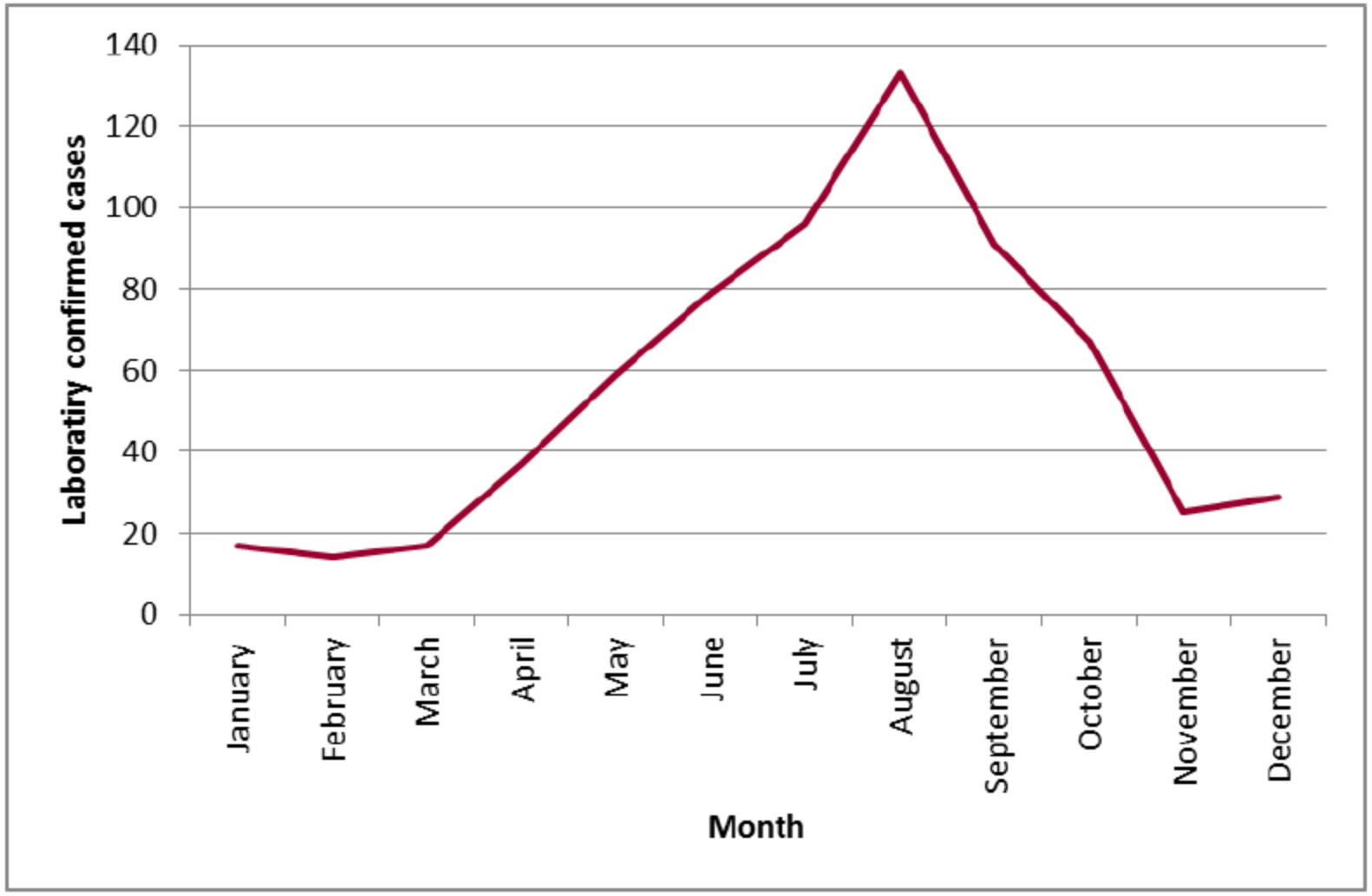


E coli **O157:H7** cases per year England and Wales

STEC epidemiology



STEC epidemiology



STEC outbreaks

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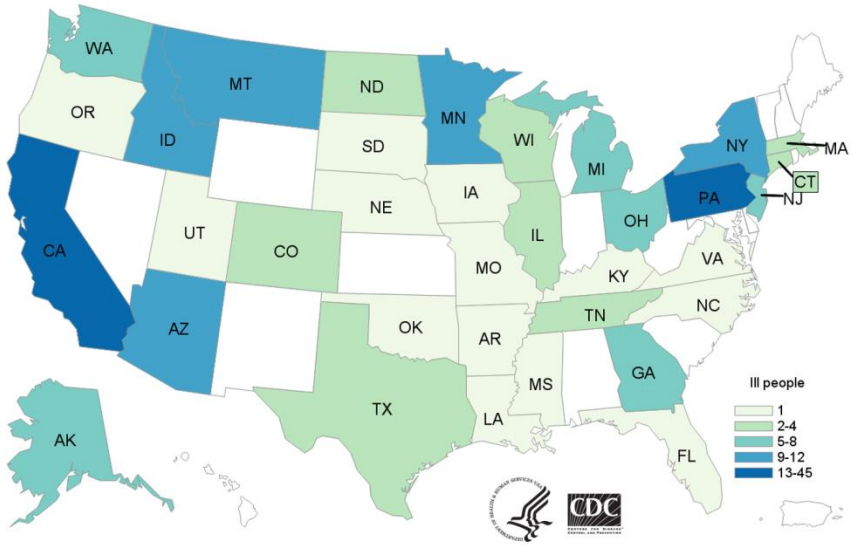
Table 3 Foodborne outbreaks of VTEC O157 in England and Wales

Agent	Total Affected	Laboratory confirmed	Hospitalised	Deaths	Setting	Food Description
VTEC O157 PT 21 | 28	15	14	10	0	Butchers	Mixed red meat and poultry meat
VTEC O157 PT 21 | 28, VT 2	22	13	5	0	Other	Private water supply
VTEC O157 PT 32	2	2	1	0	Mass catering event	Chicken and beef burgers
VTEC O157 PT8, VT2A	50	50	0	0	Multiple locations	Pre-packed salad, minced lamb

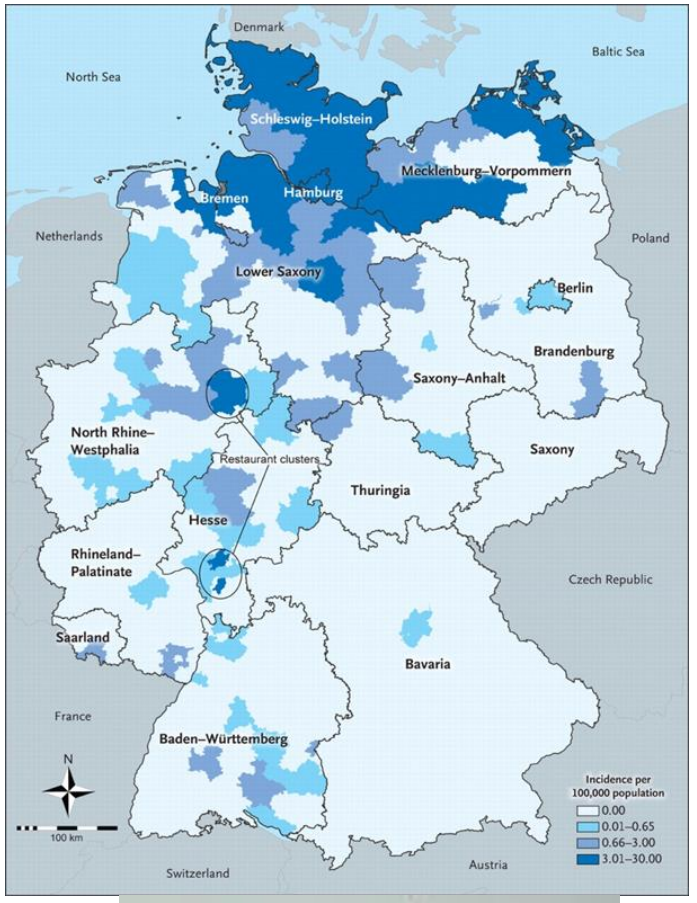
No one should die from eating salad Five people died from eating romaine lettuce in the past four months. Is the convenience of packaged salad worth the risk?

By Julia Belluz@juliaoftoronto julia.belluz@voxmedia.com Jun 4, 2018, 2:40pm EDT

Share Tweet Share



https://www.cdc.gov/ecoli/2018/o157h7-04-18/map.html



Frank NEJM 2011; Wadl Euro Surveill. 2011

Detection of STEC

- Routine stool culture will only detect E.coli O157:H7
  - Sorbitol MacConkey Agar
- Stool PCR for shiga toxin
  - Rapid
  - Detects virulence genes
  - Performed at some local laboratories and the PHE Reference Laboratory
- Serological testing

STEC epidemiology

- Detection of non-O157 STEC strains is increasing
  - O26
  - O103
  - O55 (Dorset 2014-2015 13/31 HUS)
  - O111
  - O103
  - O45
  - O104
- Increased prevalence or better detection?

Management of suspected STEC infection

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RCPCH Royal College of Paediatrics and Child Health — Leading the way in Children's Health

RC GP Royal College of General Practitioners

Health Protection Agency

The management of acute bloody diarrhoea potentially caused by vero cytotoxin-producing *Escherichia coli* in children

A guide for primary care, secondary care and public health practitioners

Diagnosis of HUS

HUS comprises microangiopathic haemolytic anaemia, thrombocytopaenia and acute renal failure. Early clinical signs may not be specific and it is recommended that the assessment of all cases of bloody diarrhoea should include the following investigations in order to identify the possible onset of HUS:

Blood	Faeces	Urine	Clinical
Full blood count and film Urea & electrolytes Liver function tests Lactate dehydrogenase C-Reactive protein Clotting screen	Culture (please ensure that the request form is marked with bloody diarrhoea as a clinical detail if present)	Microscopy Near patient (dipstick) testing for Haematuria and Proteinuria	Temperature Pulse Respiratory rate Blood pressure Weight Assessment of hydration

Treatment of VTEC

There is evidence that the best outcome of treatment of VTEC infection may be achieved by:

- Early fluid resuscitation.
- Withholding of opiate analgesia.
- Withholding of anti-motility agents.
- Withholding of non steroidal anti-inflammatory drugs (NSAIDs).
- Caution in the use of antibiotics.

July 2011

Atypical HUS (aHUS)

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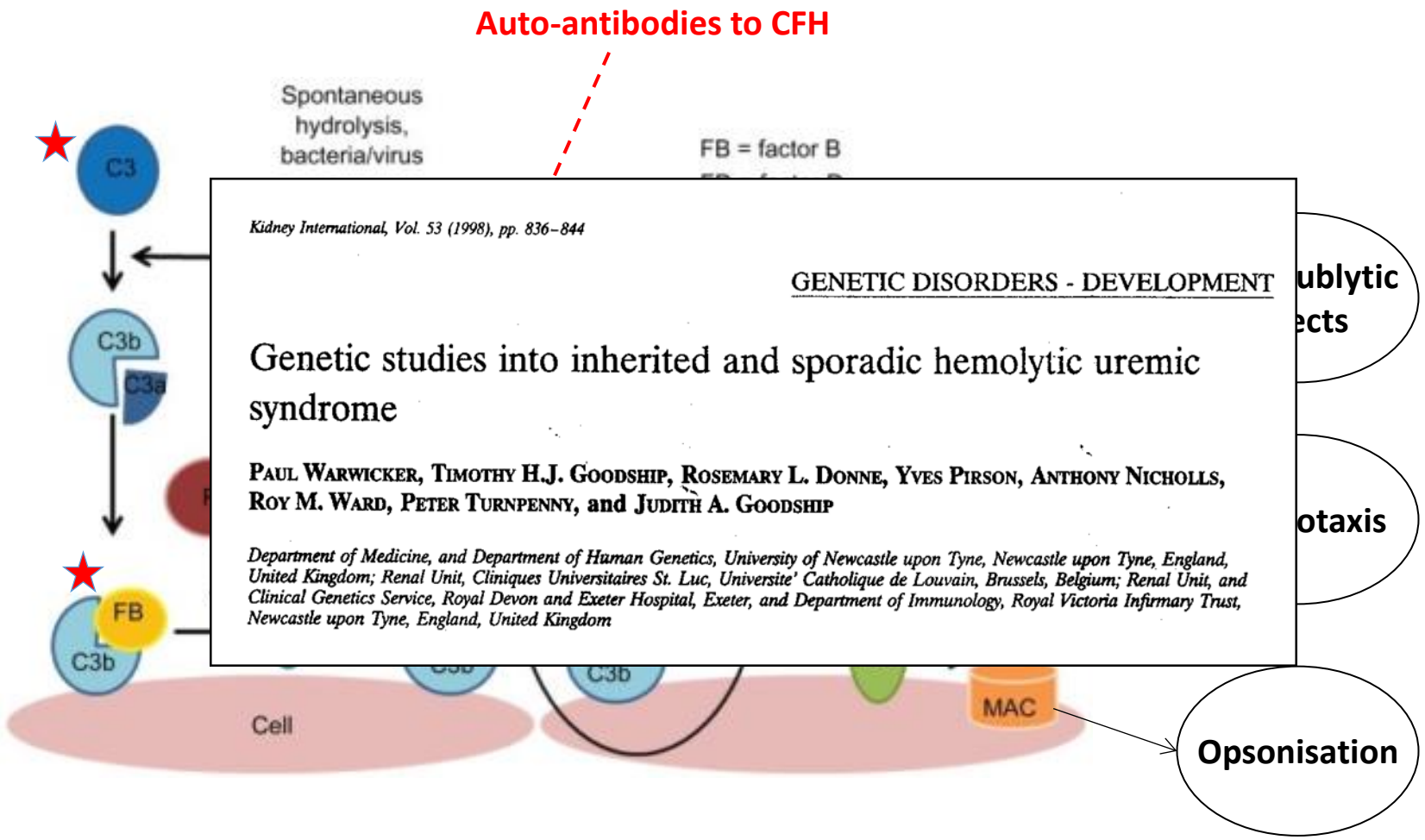
- Classical triad
  - MAHA
  - AKI
  - Thrombocytopenia
- No evidence of infection with STEC
  - May have non-bloody diarrhoea
- Relapsing
- Familial
- Progressive

Abnormalities of the alternative complement pathway cause atypical HUS (aHUS)



Kidney International, Vol. 53 (1998), pp. 836–844

GENETIC DISORDERS - DEVELOPMENT

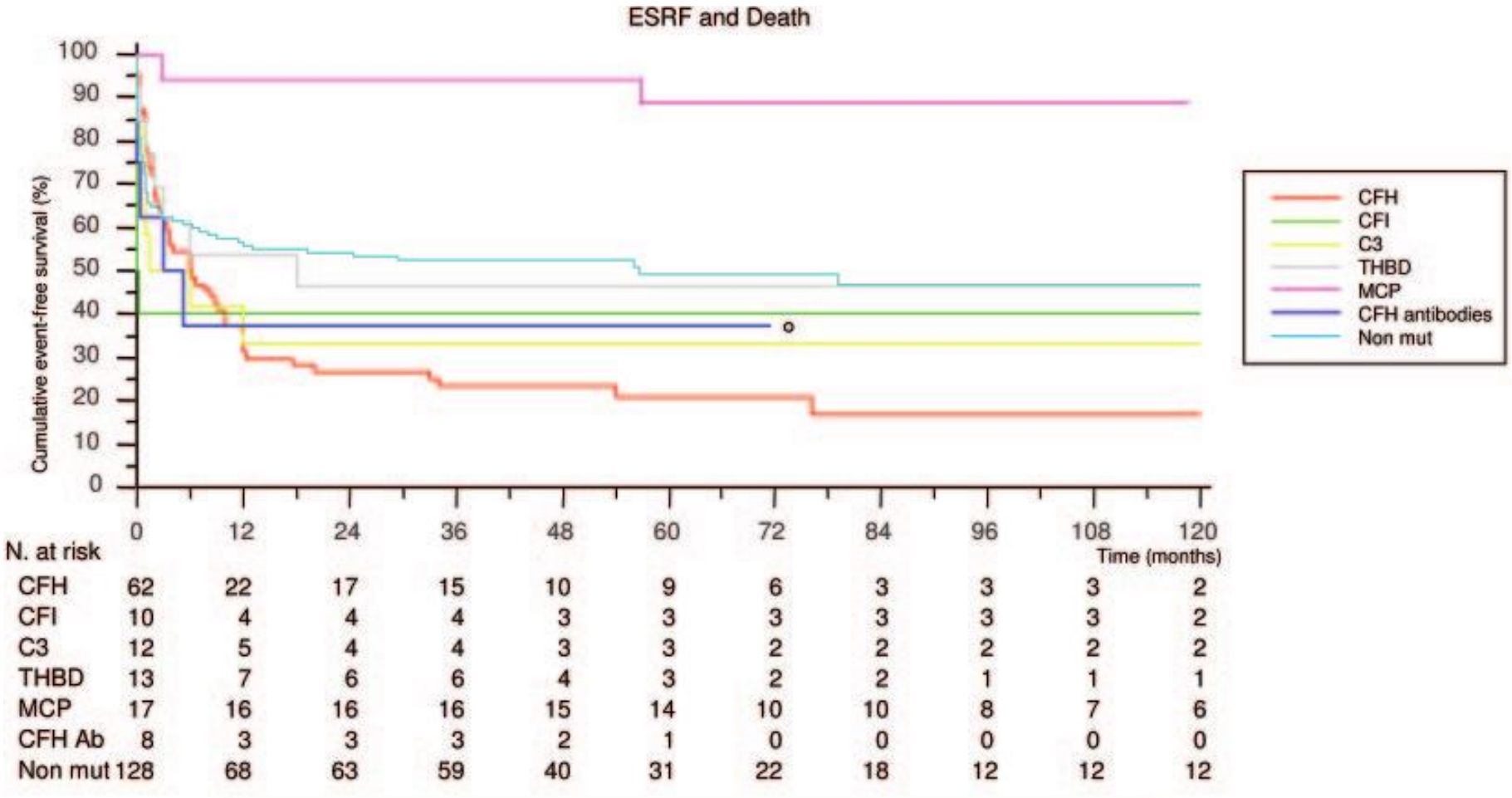
Genetic studies into inherited and sporadic hemolytic uremic syndrome

PAUL WARWICKER, TIMOTHY H.J. GOODSHIP, ROSEMARY L. DONNE, YVES PIRSON, ANTHONY NICHOLLS, ROY M. WARD, PETER TURNPENNY, and JUDITH A. GOODSHIP

Department of Medicine, and Department of Human Genetics, University of Newcastle upon Tyne, Newcastle upon Tyne, England, United Kingdom; Renal Unit, Cliniques Universitaires St. Luc, Universite' Catholique de Louvain, Brussels, Belgium; Renal Unit, and Clinical Genetics Service, Royal Devon and Exeter Hospital, Exeter, and Department of Immunology, Royal Victoria Infirmary Trust, Newcastle upon Tyne, England, United Kingdom

Abnormality	Frequency
Factor H (CFH)	24-27%
Factor I	4-8%
CD46	5-9%
C3	2-8%
Factor B	1-4%
Anti-CFH	3-6%
DGKEpsilon	<1%

aHUS had a very poor prognosis

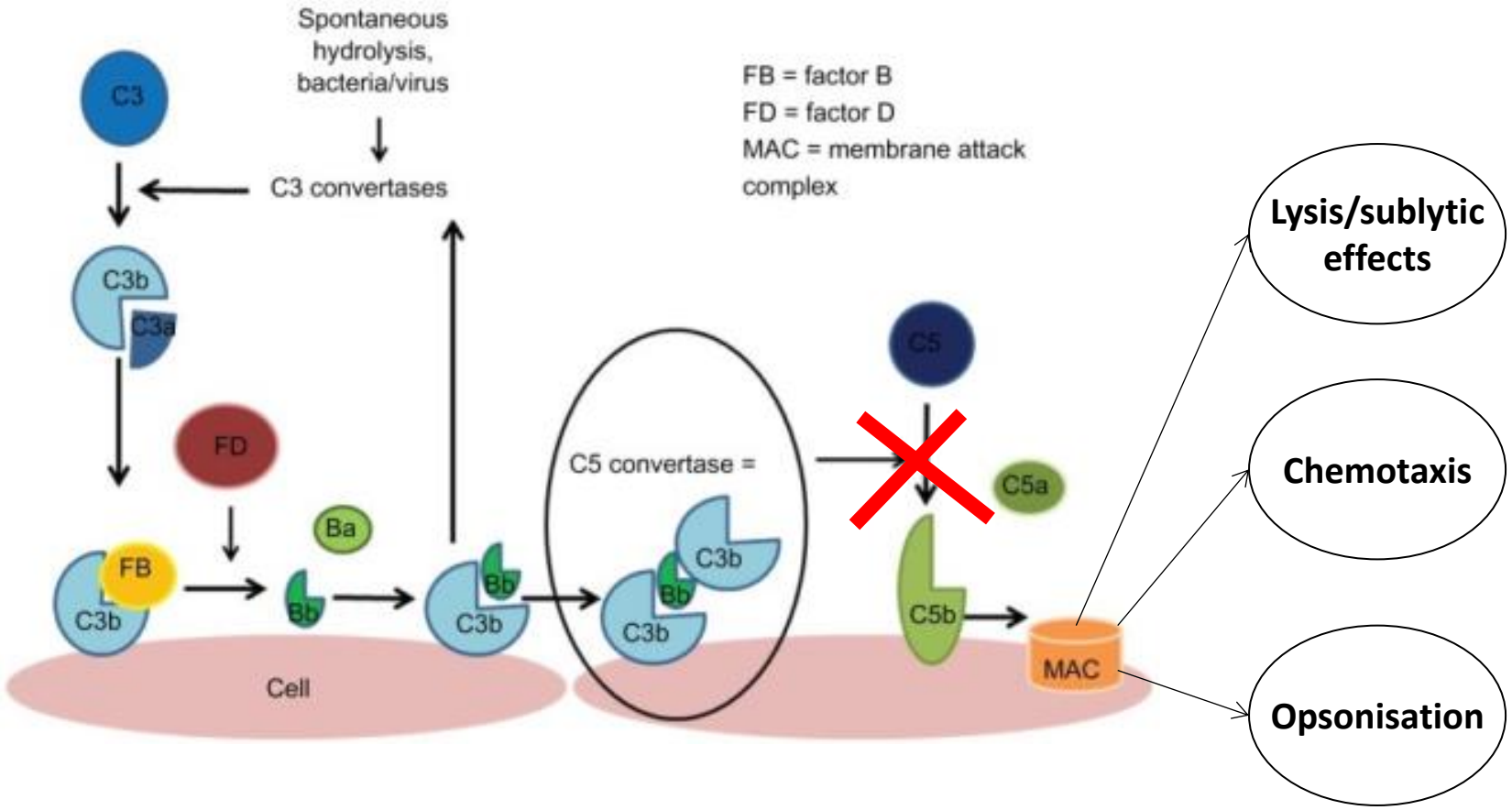


N. at risk											
CFH	62	22	17	15	10	9	6	3	3	3	2
CFI	10	4	4	4	3	3	3	3	3	3	2
C3	12	5	4	4	3	3	2	2	2	2	2
THBD	13	7	6	6	4	3	2	2	1	1	1
MCP	17	16	16	16	15	14	10	10	8	7	6
CFH Ab	8	3	3	3	2	1	0	0	0	0	0
Non mut	128	68	63	59	40	31	22	18	12	12	12

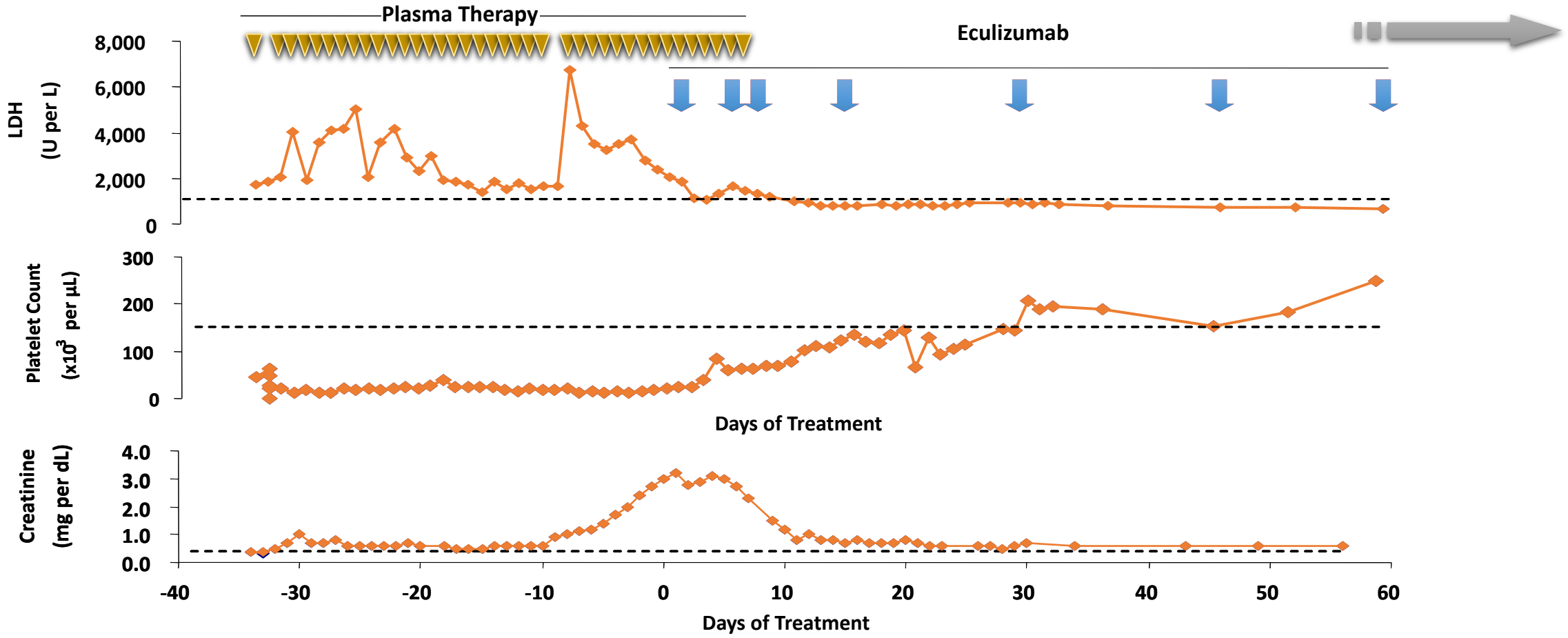
Cumulative Kaplan-Meier estimates of the rates of first event (ESRF or death).

Noris et al, Clin J Am Soc Nephrol 2010

Eculizumab

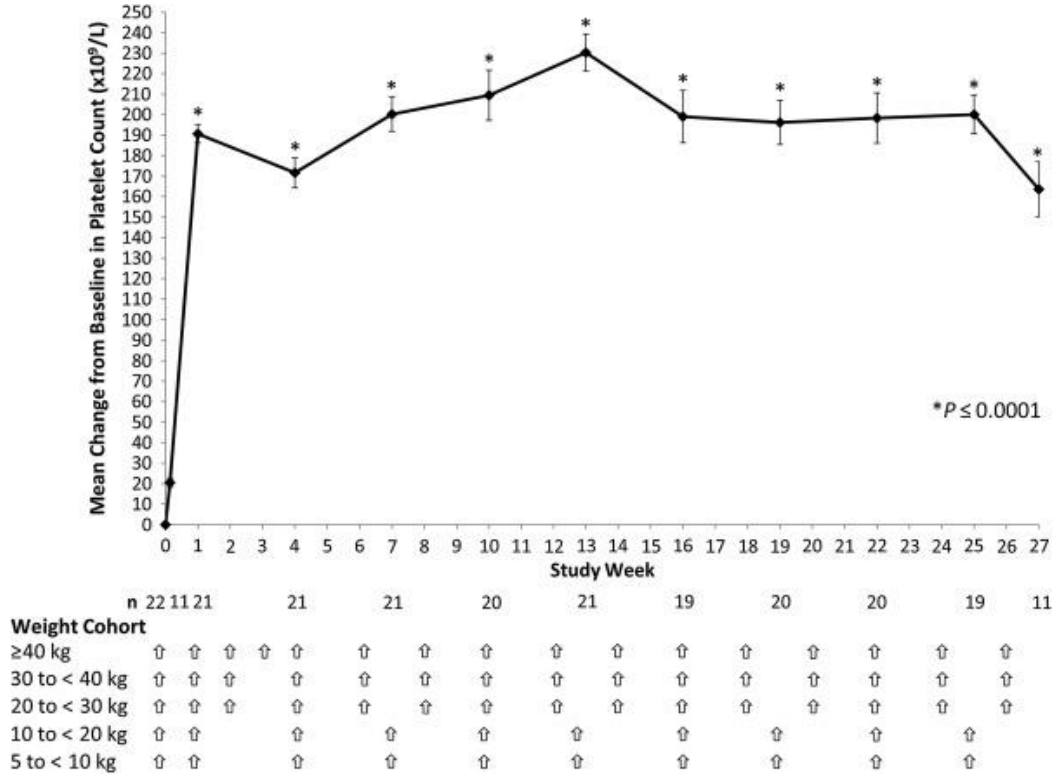

Spontaneous hydrolysis, bacteria/virus
C3
C3 convertases
FB = factor B
FD = factor D
MAC = membrane attack complex
C3b
C3a
FD
FB
C3b
Ba
Bb
C3b
Bb
C5 convertase =
C3b
Bb
C3b
C5
C5a
C5b
MAC
Cell
Lysis/sublytic effects
Chemotaxis
Opsonisation

Case report



Gruppo RA, et al. *N Engl J Med.* 2009;360(5):544-6.

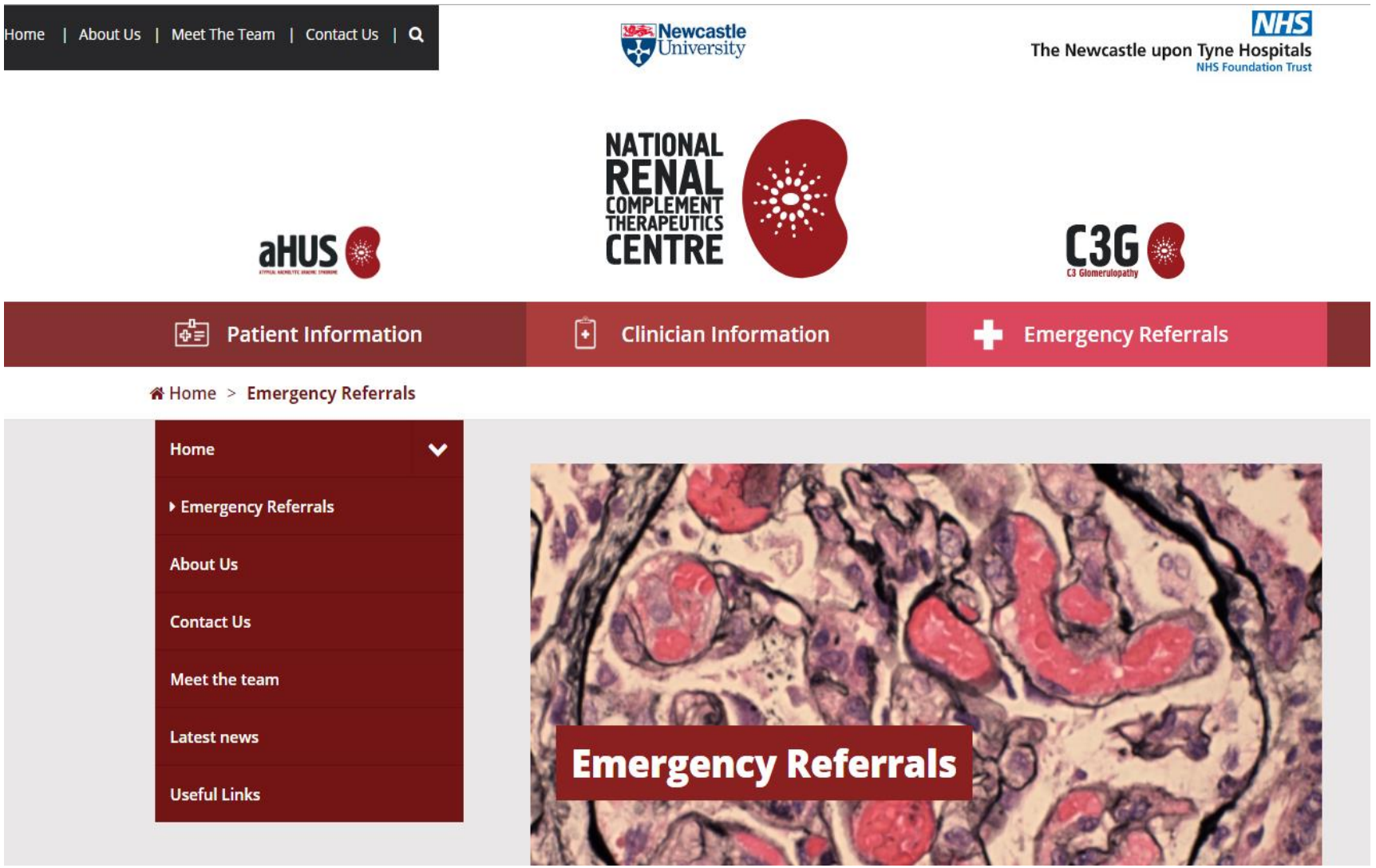
Eculizumab is a safe and effective treatment in pediatric patients with aHUS



Improvement in platelet count over 27 weeks of eculizumab treatment

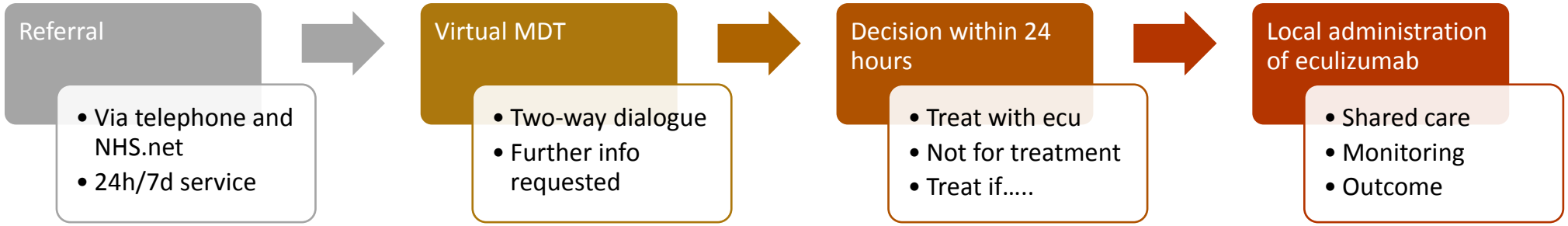
Larry A. Greenbaum, Marc Fila, Gianluigi Ardissino, Samhar I. Al-Akash, Jonathan Evans, Paul Henning, Kenneth V. Lieberman, Silvio Maringhini, Lars Pape, Lesley Rees, Nicole C.A.J. van de Kar, Johan Vande Walle, Masayo Ogawa, Camille L. Bedrosian, Christoph Licht. Kidney International, Volume 89, Issue 3, 2016, 701–711

Access to eculizumab for aHUS in England



www.atypicalhus.org.uk

Process for application for eculizumab



Samples sent urgently via courier
ADAMTS13
STEC investigations
Complement genetics and autoantibodies
Complement activation markers

- Since April 2013
  - 94 paediatric referrals
  - 46 commenced upon eculizumab

STEC testing

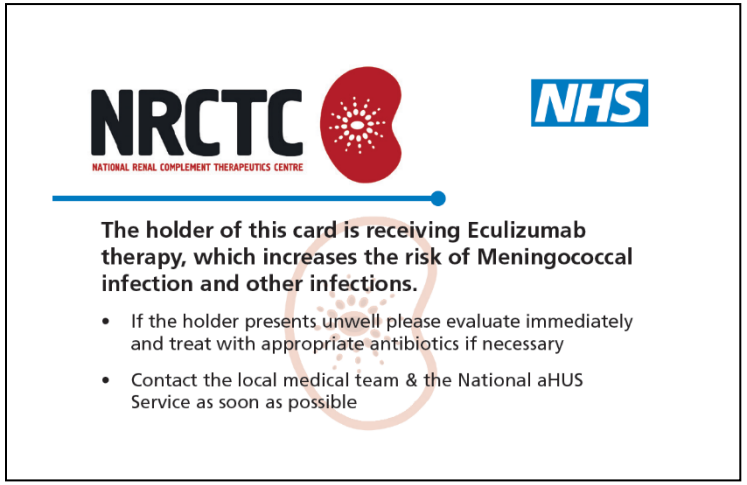
- Samples MUST be sent to Public Health England Reference laboratory at Colindale
- **For just a single patient, sending appropriate specimens and liaising with microbiology could ultimately save the NHS millions of pounds!!!**

Claire Jenkins
Head of *E. coli* Reference Service
Public Health England

Meningococcal Sepsis Prevention

- Meningococcal vaccination mandatory
  - Tetravalent (ACWY)
  - Bexsero
- Vaccination Titres at 1 month
  - Revaccinate as required
- Prophylactic antibiotics
- Patient awareness

Prof Ray Burrow
Vaccine Evaluation Unit, Manchester



Eculizumab in STEC HUS

NATIONAL RENAL COMPLEMENT THERAPEUTICS CENTRE

Eculizumab in Severe Shiga-Toxin–Associated HUS

TO THE EDITOR: The hemolytic–uremic syndrome (HUS), a thrombotic microangiopathy, most commonly occurs secondary to infection with Shiga-toxin–producing *Escherichia coli* (STEC-HUS), although rare, atypical forms are associated with abnormalities in complement-regulating proteins. The inhibition of terminal complement complex formation by the monoclonal C5 antibody eculizumab has recently been reported as a treatment for atypical HUS.[1]

We report on three 3-year-old patients with severe STEC-HUS that required hemodialysis. In Patient 1, plasma exchanges were performed because of low C3 and elevated C3d serum concentrations, which suggested complement activation. Plasma exchange was also performed in Patient 2 because of severe central nervous system involvement, a rare complication that often leads to death or permanent neurologic damage.[2] Progressive involvement of the central nervous system developed in both patients despite 5 consecutive days of plasma exchange.

Given the devastating prognosis, we administered eculizumab to these two patients, as well as to a third patient with a similar disease course, at 7-day intervals, twice in Patients 1 and 3 and four times in Patient 2. The neurologic status in all three patients improved dramatically within 24 hours after the first eculizumab infusion. let counts normalized, and lactate dehydrogenase levels decreased within 5 days in all patients (Fig. 1, and the Supplementary Appendix, available with the full text of this letter at NEJM.org).

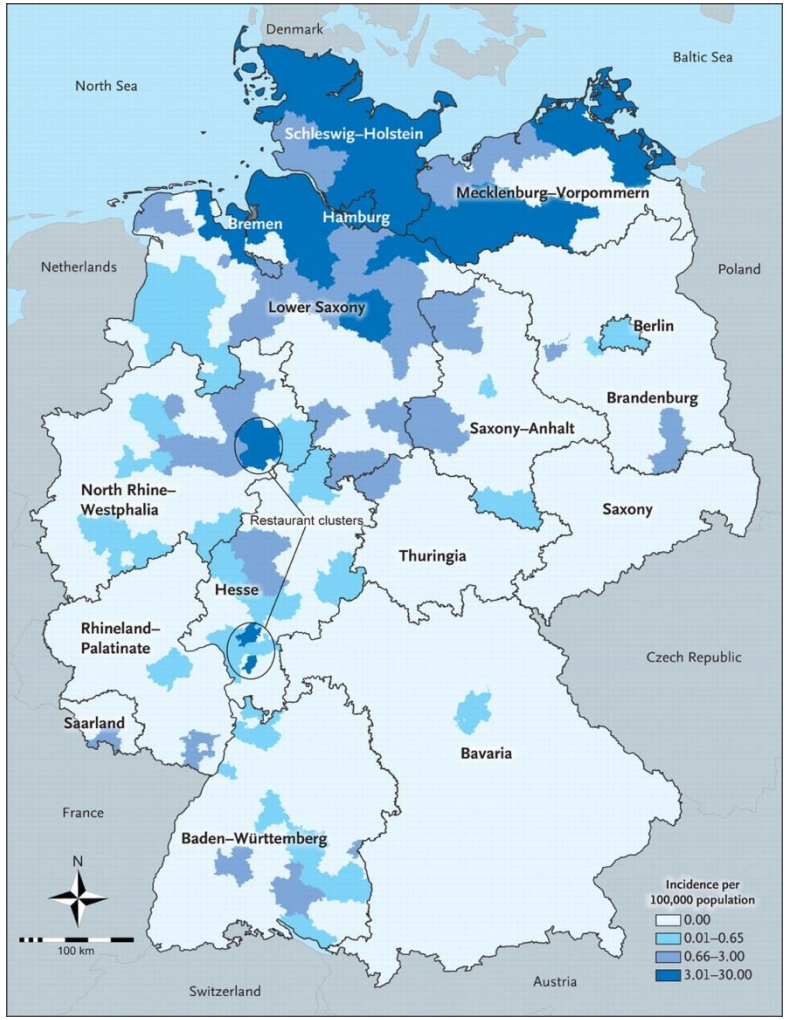
Dialysis was discontinued after 3 days in Patient 1, after 16 days in Patient 2, and after 13 days in Patient 3, and the patients were discharged with apparently normal neurologic status 9, 35, and 20 days, respectively, after the administration of the first dose of eculizumab. Renal function fully recovered, with mild residual proteinuria and hypertension in Patients 1 and 3. All patients have remained in full remission for the past 6 months. Screening for mutations in the genes encoding complement regulatory proteins (*CFH*, *CFI*, *MCP*, *C3*, *CFB*, and *THBD*) and testing for anti-CFH antibodies were negative in all patients.

In the cases reported here, spontaneous recovery seemed unlikely, given the rapidly progressive course of the disease. The rapid clinical response to eculizumab in all three children supports the concept that Shiga toxin may activate complement directly,[3] providing a rationale for therapeutic complement blockade in STEC-HUS with severe complications. Complement hyperactivation was recently demonstrated in STEC-HUS,[4] and a mutation in the complement-regulating gene *MCP* was reported in a fatal case of STEC-HUS.[5] The dramatic resolution of symptoms after

Lapeyraque
NEJM May 2011

German outbreak 2011

- 3816 STEC cases
- 845 (22%) developed HUS
- 54 deaths
- 88% HUS cases were adults
- E coli O104:H4
- Rapidly convened industry sponsored trial of eculizumab



Frank NEJM 2011; Wadl Euro Surveill. 2011

The ECUSTEC trial

Eculizumab in Shiga-Toxin producing E. Coli Haemolytic Uraemic Syndrome (ECUSTEC): A Randomised, Double-Blind, Placebo-Controlled Trial

Research Objectives:

- To determine whether the severity of STEC HUS is less in those given Ecu compared to those given placebo
- To assess the safety of Ecu in STEC HUS
- To determine whether the incidence of CKD following STEC HUS is less in those receiving Ecu compared with those receiving placebo
- To evaluate the cost-effectiveness of administration of Ecu in STEC HUS from the perspective of the NHS

The ECUSTEC trial

- 134 children over 4 years
- Children aged 6m to 18y
- Diagnosis of HUS
  - MAHA
  - Thrombocytopenia (platelets <150x10^9/l)
  - AKI “injury” or “failure” category of pRIFLE criteria* despite correction of hypovolaemia
- Diarrhoea within 14 days
- All paediatric nephrology units in England, Wales & Scotland
- Patient identification centres

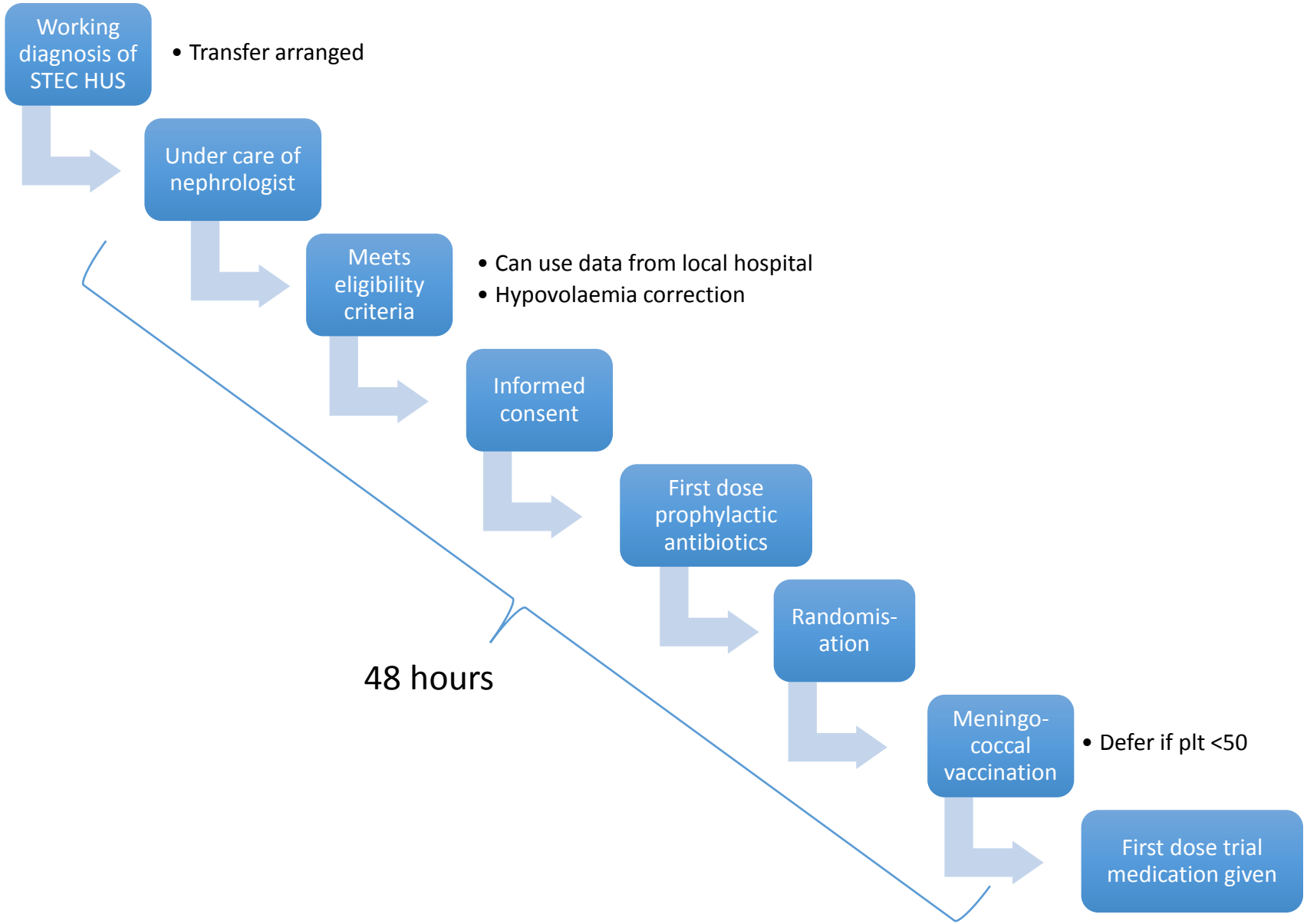
https://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/renal/ECUSTEC/index.aspx

The ECUSTEC trial - PIC

- Patient identification centres (PIC) have a key role in the trial
- Local hospitals where patients typically present and are diagnosed and stabilised
- Early identification of potential patients
- Liaison with renal unit
- Provide families with brief information about the trial prior to transfer
  - Specific patient information sheet
- 65 have confirmed capacity and capability
- 100+ have been contacted
- ecustec@trials.bham.ac.uk

https://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/renal/ECUSTEC/index.aspx

The ECUSTEC trial



Placebo arm

Standard therapy
+
Day 1 Placebo
Day 8 Placebo
+
Antibiotic prophylaxis

Active arm

Standard therapy
+
D1 Eculizumab
D8 Eculizumab
+
Antibiotic prophylaxis

Pharmacy staff unblinded

All other staff & BCTU are blinded

Blinded label
MHRA approved label text and template to be used

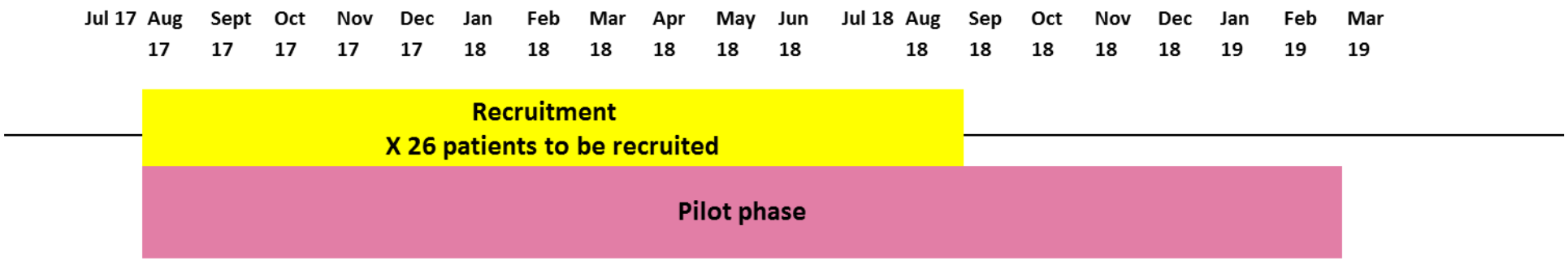
Renal	Lowest eGFR >50	1
	Lowest eGFR 26-50, no oligoanuria*	2
	Lowest eGFR ≤ 25, no oligoanuria*	3
	Oligoanuria* but no dialysis (or renal replacement therapy, RRT) required	4
	Dialysis/RRT <48 hours	5
	Dialysis/RRT 2 days	6
	Dialysis/RRT 3 days	7
	Dialysis/RRT 4 days	8
	Dialysis/RRT 5 days	9
	Dialysis/RRT 6 days	10
	Dialysis/RRT 7 days	11
	Dialysis/RRT 8 days	12
	Dialysis/RRT 9 days	13
	Dialysis/RRT 10 days	14
	Dialysis/RRT 11 days	15
	Dialysis/RRT 12 to 13 days	16
	Dialysis/RRT 14 to 17 days	17
	Dialysis/RRT 18 to 20 days	18
	Dialysis/RRT 21 to 27 days	19
	Dialysis/RRT 28 to 34 days	20
	Dialysis/RRT 35 to 41 days	21
	Dialysis/RRT 42 to 48 days	22
	Dialysis/RRT 49 to 55 days	23
	Dialysis/RRT >55 days	24
CNS	No obvious CNS involvement	0
	Altered consciousness (Agitation, irritability, hallucinations, confusion, excessive drowsiness)	2
	Single seizure	4
	Two or more seizures 24 hrs apart**	6
	Transient focal neurological defect (>24 hrs*** but <1 week)	7
	Persistent focal neurological defect (present at day 60 and persistent for more than 1 week)	10
	Persistent global (≥ 2 brain functions - vision/hearing/cognitive/motor/sensory/memory) neurological defect at day 60	15
Pancreas	No clinical or biochemical evidence pancreatitis	0
	Raised amylase and/or lipase† without clinical symptoms/signs	2
	Hyperglycaemia without insulin requirement	6
	Pancreatitis with sequelae (laparotomy, parenteral nutrition††, insulin required)	8
	Chronic sequelae of pancreatitis at day 60 (parenteral nutrition††, insulin, other)	10
Gastro-intestinal	No abdominal surgery reguired (except related to peritoneal dialysis catheter)	0
	Laparoscopy/laparotomy required for abdominal symptoms	5
	Intestinal perforation AND/OR bowel resection required	8
	Stoma formation	10
Cardiac	No cardiac involvement (normal CVS examination - except hypertension/volume overload)	0
	Cardiac failure confirmed by ECHO††† (impaired systolic ventricular function or chamber enlargement or valve regurgitation)	4
	Cardiac failure confirmed by ECHO with dilated cardiomyopathy	6
	Myocardial infarction (on standard ECG +/- troponin +/- ECHO evidence)	10

Primary outcome measure

Clinical severity score

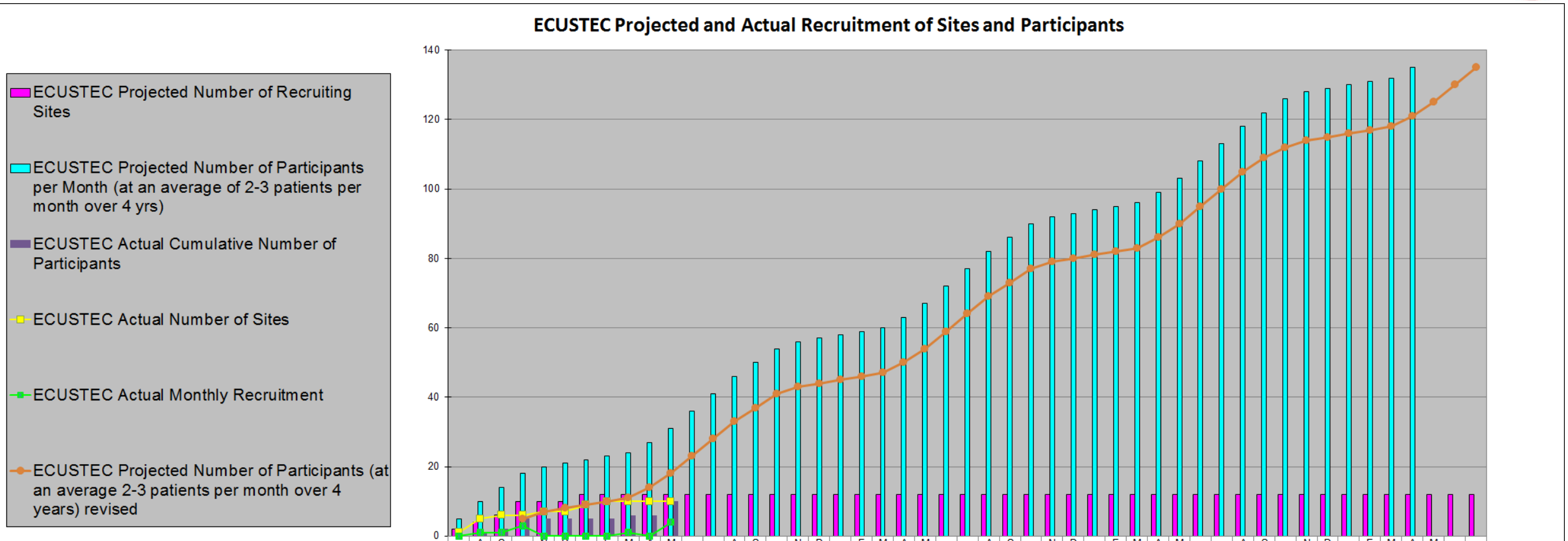
assigned following D60 assessments

The ECUSTEC trial



- Pilot recruitment phase is included in the trial
- Need to recruit total of 26 patients by November 2018
- And to demonstrate retention in trial

Recruitment



	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21
ECUSTEC Projected Number of Recruiting Sites	2	4	6	10	10	10	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
ECUSTEC Projected Number of Participants per Month (at an average of 2-3 patients per month over 4 yrs)	5	10	14	18	20	21	22	23	24	27	31	36	41	46	50	54	56	57	58	59	60	63	67	72	77	82	86	90	92	93	94	95	96	99	103	108	113	118	122	126	128	129	130	131	132	135			
ECUSTEC Actual Cumulative Number of Participants	0	1	2	5	5	5	5	5	6	6	10																																						
ECUSTEC Actual Number of Sites	1	5	6	6	7	7	9	10	10	10	10																																						
ECUSTEC Actual Monthly Recruitment	0	1	1	3	0	0	0	0	1	0	4																																						
ECUSTEC Projected Number of Participants (at an average 2-3 patients per month over 4 years) revised				5	7	8	9	10	11	14	18	23	28	33	37	41	43	44	45	46	47	50	54	59	64	69	73	77	79	80	81	82	83	86	90	95	100	105	109	112	114	115	116	117	118	121	125	130	135

On going trials

- ECULISHU – France
  - Eculizumab 5 doses
  - Severe patients not included
  - Primary outcome measure renal only
- ZITHROSHU – France
  - Azithromycin

Key take home messages

- HUS remains a significant cause of morbidity and mortality
- Differentiating STEC HUS from aHUS is important
- STEC testing requires liaison with microbiology colleagues
- In confirmed or suspected STEC infection
  - Notify public health
  - Ensure good hydration
  - Avoid anti-motility agents and antibiotics
  - Be vigilant for HUS development
- Research has transformed the management of aHUS
- Ongoing trials examining role of eculizumab in STEC HUS
- ECUSTEC is recruiting now
  - Is your site a PIC?
  - Early conversation with nephrology unit

Acknowledgements

- Birmingham Clinical Trials Unit
- NIHR Efficacy and Mechanism Evaluation

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