Sindrome emolitico uremica e infezioni

F. Baldelli

Perugia, 29.09.2016

Microangiopatie trombotiche (TMA) e Infezioni

Sindrome emolitico – uremica

HUS

- Insufficienza renale
- Anemia emolitica
- Trombocitopenia

- (30% + febbre e disturbi SNC)

Porpora trombotica trombocitopenica

TTP

- Anemia emolitica
- Trombocitopenia
- Disturbi SNC
- Insufficienza renale
- Febbre

(60% assenza di 1-2 segni)

Differential Diagnosis Between DIC and TMA

	DIC	TMA
Platelet count	↓	↓
Fibrinogen	↓	Normal
Fibrinogen degradation products	↑	Normal
D-dimers	↑	Normal
Antithrombin	↓	Normal
Schystocytes	+	+++
Clotting times	Prolonged	Normal
BLOOD PRESSURE	↓↓↓	↑↑↑

Nearly all TMAs present a non-immune hemotylic anemia !!

HUS
(ADAMTS 13 NORMALE)

TTP
ADAMTS 13 ↓

Stx+ 85-90%

↓

S. *dysenteriae* 1
Stx 1 Stx 2

STEC

(Shiga toxin *E.coli*)

a HUS (10-15%) Stx -

familiare
(anomalie complemento)
FH, FI, CD46, ...

sporadiche
.....
.....
infezioni
(40%
S. pneumoniae
Sp-HUS)

infezioni come
trigger

Congenita

Acquisita
(inibitori autoimmuni
ADAMTS 13)
Infezioni ?

Elementi clinici orientativi per HUS

a) **Bambino < 5 aa** vs adulto
b) Interessamento rene vs SNC
c) Forma epidemica vs forma sporadica

Epidemiol. Infect. (2008), **136**, 577–603. © 2007 Cambridge University Press
doi:10.1017/S0950268807009351 Printed in the United Kingdom

REVIEW ARTICLE

Part II. Analysis of data gaps pertaining to *Shigella* infections in low and medium human development index countries, 1984–2005

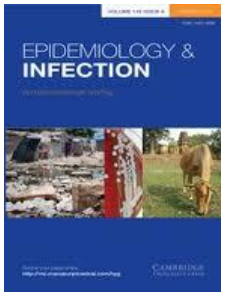
P. K. RAM[1,2*], J. A. CRUMP[2], S. K. GUPTA[2], M. A. MILLER[3] AND E. D. MINTZ[2]

[1] *School of Public Health and Health Professions, University at Buffalo, Buffalo, NY, USA*
[2] *Enteric Diseases Epidemiology Branch, National Center for Zoonotic, Vectorborne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA*
[3] *Fogarty International Center, National Institutes of Health, Bethesda, MD, USA*

(*Accepted 30 June 2007; first published online 9 August 2007*)

Stx + HUS

Shigellosi



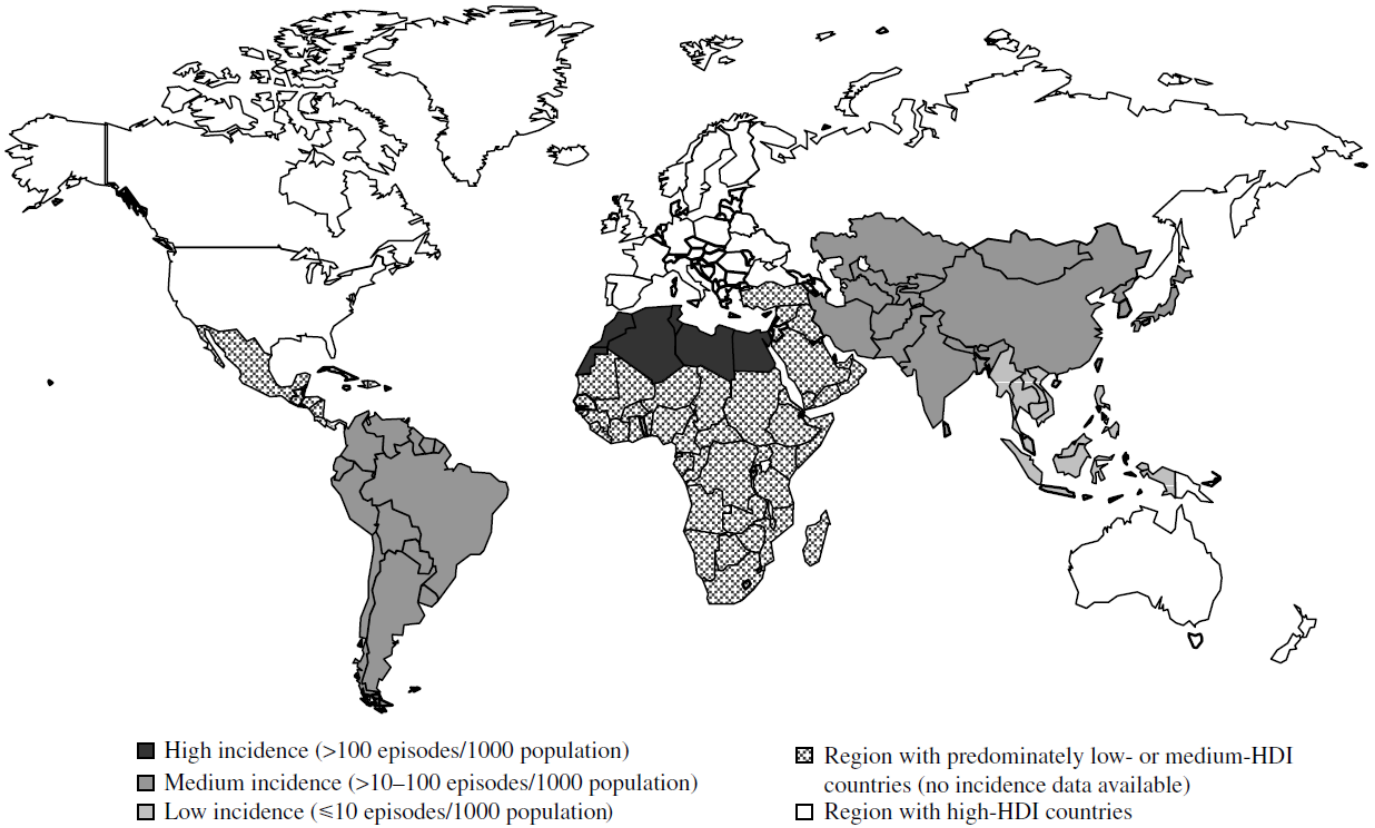


Fig. 1. Incidence of shigellosis, by geographic region, 1984–2005. Countries contributing incidence data: China [5], Thailand [6], Egypt [7], Bangladesh [8] and Brazil [9].

Stx + HUS

S. dysenteriae

World Health Organization

Global burden of *Shigella* infections: implications for vaccine development and implementation of control strategies

K.L. Kotloff,[1] J.P. Winickoff,[2] B. Ivanoff,[3] J.D. Clemens,[4] D.L. Swerdlow,[5] P. J. Sansonetti,[6] G.K. Adak,[7] & M.M. Levine[8]

Few studies provide data on the global morbidity and mortality caused by infection with *Shigella* spp.; such estimates are needed, however, to plan strategies of prevention and treatment. Here we report the results of a review of the literature published between 1966 and 1997 on *Shigella* infection. The data obtained permit calculation of the number

The annual number of *Shigella* episodes throughout the world was estimated to be 164.7 million, of which 163.2 million were in developing countries (with 1.1 million deaths) and 1.5 million in industrialized countries. A total of 69% of all episodes and 61% of all deaths attributable to shigellosis involved children under 5 years of age. The median percentages of isolates of *S. flexneri*, *S. sonnei*, *S. boydii*, and *S. dysenteriae* were, respectively, 60%, 15%, 6%, and 6% (30% of *S. dysenteriae* cases were type 1) in developing countries; and 16%, 77%, 2%, and 1% in

Shigellosi

- Portatori: uomo e alcuni primati
- **Trasmissione inter-umana** : diretta, indiretta
  scarsa igiene (acqua, insalate crude, prodotti caseari....)

- Infezione anche con **10** colonie !. *S. dysenteriae* resiste PH acido gastrico

- Tendenza a **invadere** gli strati della sottomucosa ⟶ ulcerazioni

- Incubazione 12 - 96 ore.

  Febbre, diarrea infiammatoria e sanguinolenta, disidratazione.

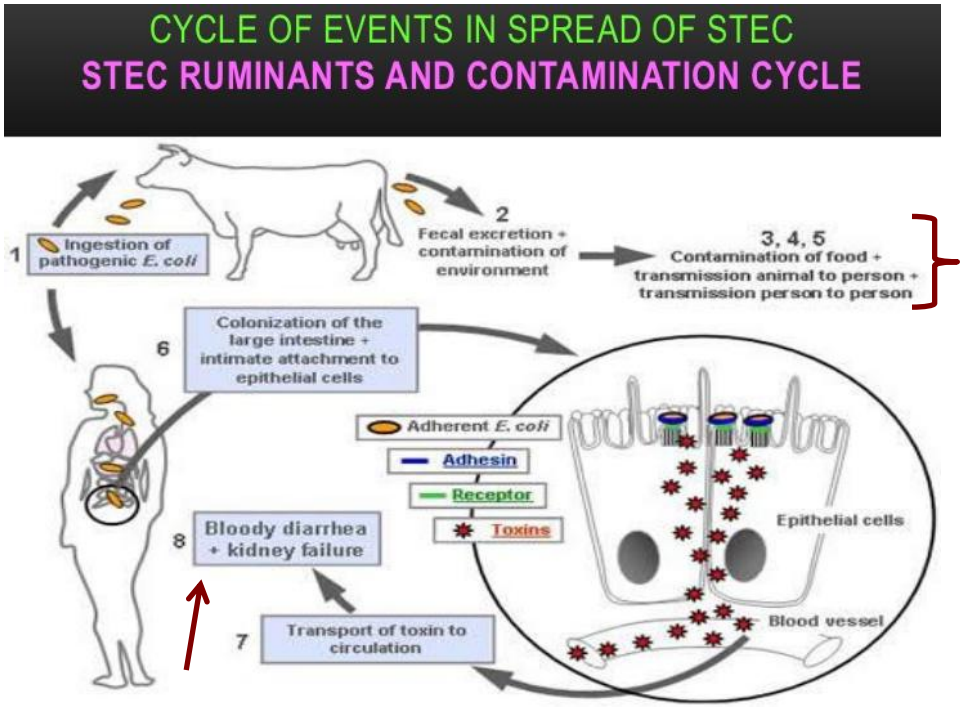
  Decorso 4-7 gg

- Complicanze : artriti reattive, Sindrome di Reiter, **HUS**

STEC-HUS

STEC : E. coli produttrice di tossina Shiga-like (Stx +)

- *Escherichia coli* Stx + ceppi 0157:H7 e ceppi non-0157:H7 → → STEC (appartengono a *E. coli enteroemorragica* : EHEC)
- Patogeni responsabili di zoonosi (portatori ruminanti, uomo)



STEC - HUS

Epidemie di gastroenterite da O 157 : H7 (U.S.) e modalità di trasmissione

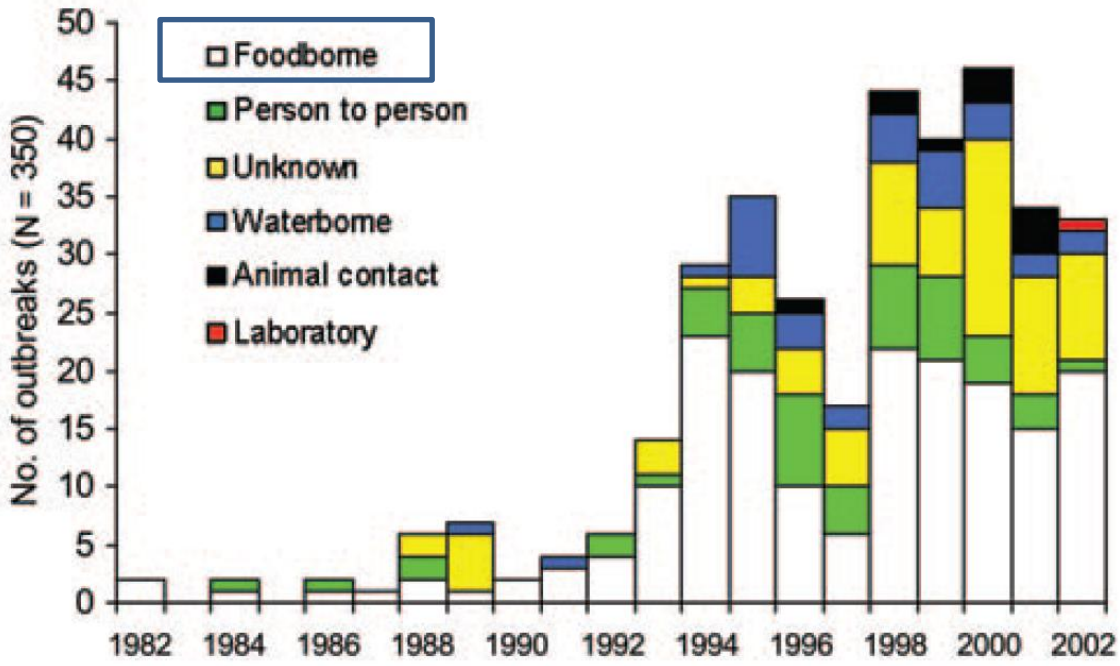


Figure 3. Transmission routes of *Escherichia coli* O157 outbreaks by year.

Rischio maggiore in età pediatrica (<5aa)

Rischio HUS in età < 10 aa: circa 15%

STEC O157: H7 (U.S.)

Foodborne Transmission

RESEARCH

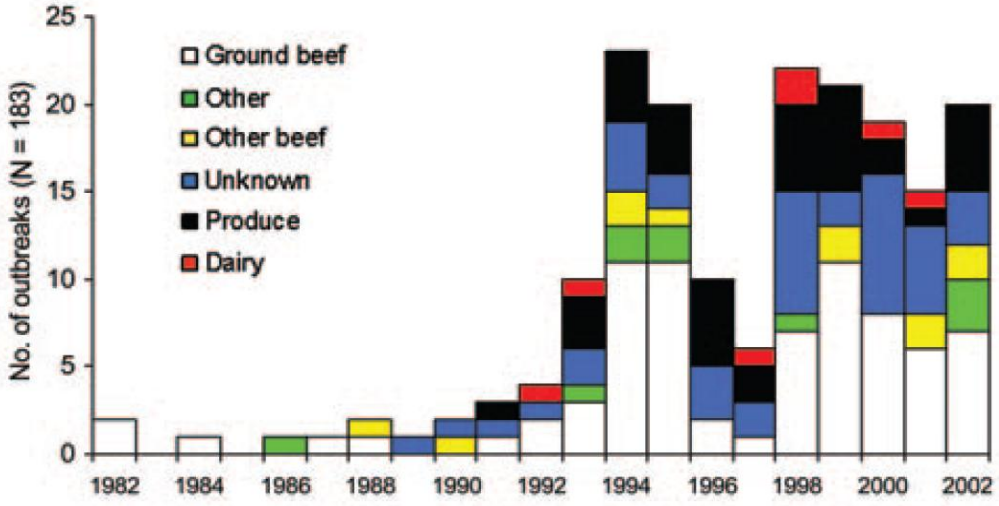


Figure 4. Vehicles of foodborne *Escherichia coli* O157 outbreaks by year.

EUROPA
Epidemie di gastroenterite

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Epidemic Profile of Shiga-Toxin–Producing *Escherichia coli* O104:H4 Outbreak in Germany

Christina Frank, Ph.D., Dirk Werber, D.V.M., Jakob P. Cramer, M.D.,

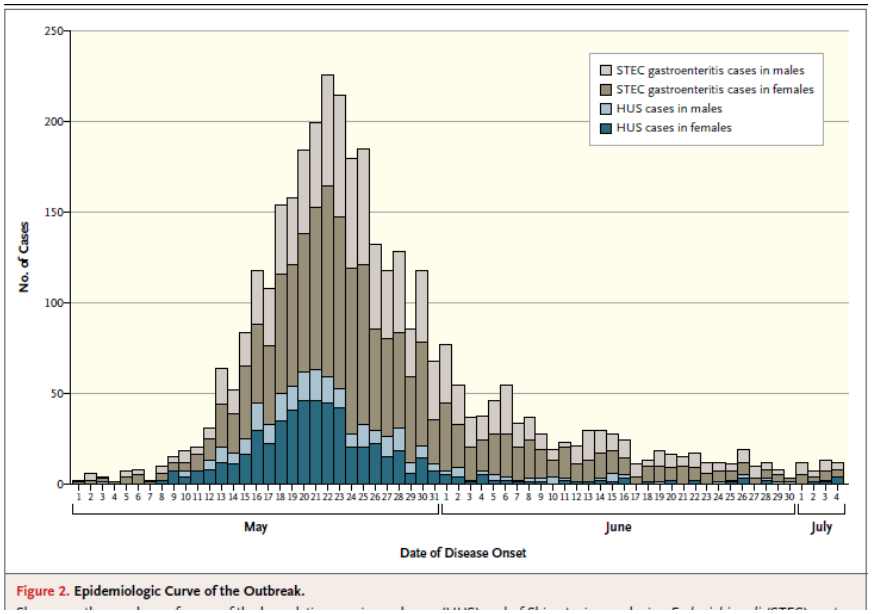


Figure 2. Epidemiologic Curve of the Outbreak.

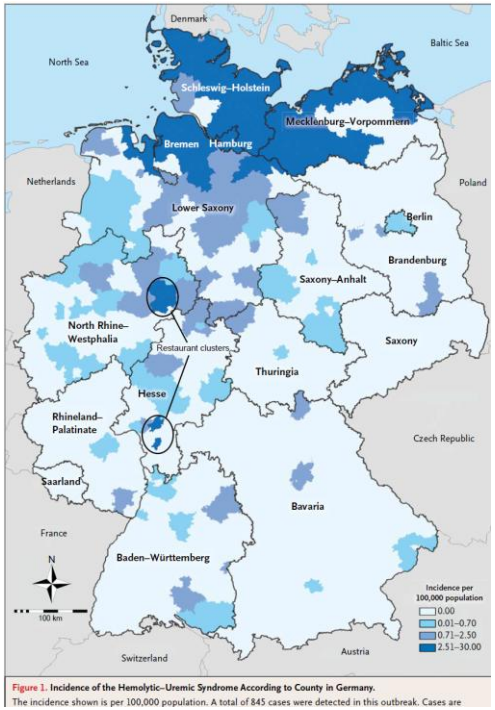


Figure 1. Incidence of the Hemolytic–Uremic Syndrome According to County in Germany.
The incidence shown is per 100,000 population. A total of 845 cases were detected in this outbreak. Cases are

CONCLUSIONS

In this outbreak, caused by an unusual *E. coli* strain, cases of the hemolytic–uremic syndrome occurred predominantly in adults, with a preponderance of cases occurring in women. The hemolytic–uremic syndrome developed in more than 20% of the identified cases.

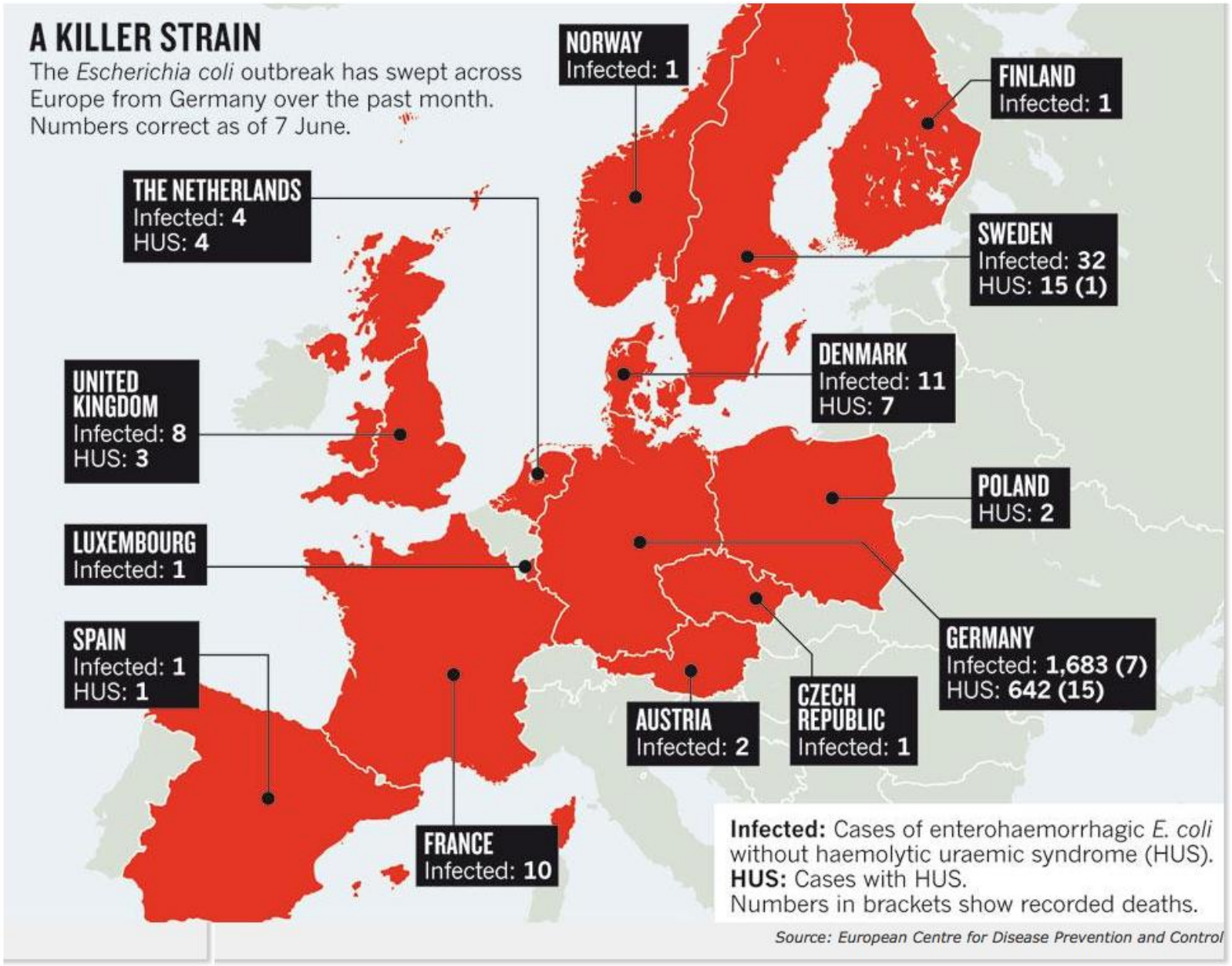
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Epidemic Profile of Shiga-Toxin–Producing *Escherichia coli* O104:H4 Outbreak in Germany

Christina Frank, Ph.D., Dirk Werber, D.V.M., Jakob P. Cramer, M.D.,

- 1 Maggio - 4 Luglio 2011 *E. coli* O104:H4 **ESBL +**
- Casi 3816 (esposizione a germogli crudi ?)
- HUS 845 (**88% adulti**)
- Decessi 54 (6.4%)
- Incubazione a HUS 8gg, onset a HUS 5gg
- No febbre (> 38.5° C)
- Diarrea emorragica **64% bambini , 91% adulti**
- **Dolori addominali 100 %.**


A KILLER STRAIN
The Escherichia coli outbreak has swept across Europe from Germany over the past month. Numbers correct as of 7 June.
NORWAY
Infected: 1
FINLAND
Infected: 1
THE NETHERLANDS
Infected: 4
HUS: 4
SWEDEN
Infected: 32
HUS: 15 (1)
DENMARK
Infected: 11
HUS: 7
UNITED KINGDOM
Infected: 8
HUS: 3
POLAND
HUS: 2
LUXEMBOURG
Infected: 1
SPAIN
Infected: 1
HUS: 1
GERMANY
Infected: 1,683 (7)
HUS: 642 (15)
AUSTRIA
Infected: 2
CZECH REPUBLIC
Infected: 1
FRANCE
Infected: 10
Infected: Cases of enterohaemorrhagic E. coli without haemolytic uraemic syndrome (HUS).
HUS: Cases with HUS.
Numbers in brackets show recorded deaths.
Source: European Centre for Disease Prevention and Control

Laboratory preparedness for detection and monitoring of Shiga toxin 2-producing *Escherichia coli* O104:H4 in Europe and response to the 2011 outbreak

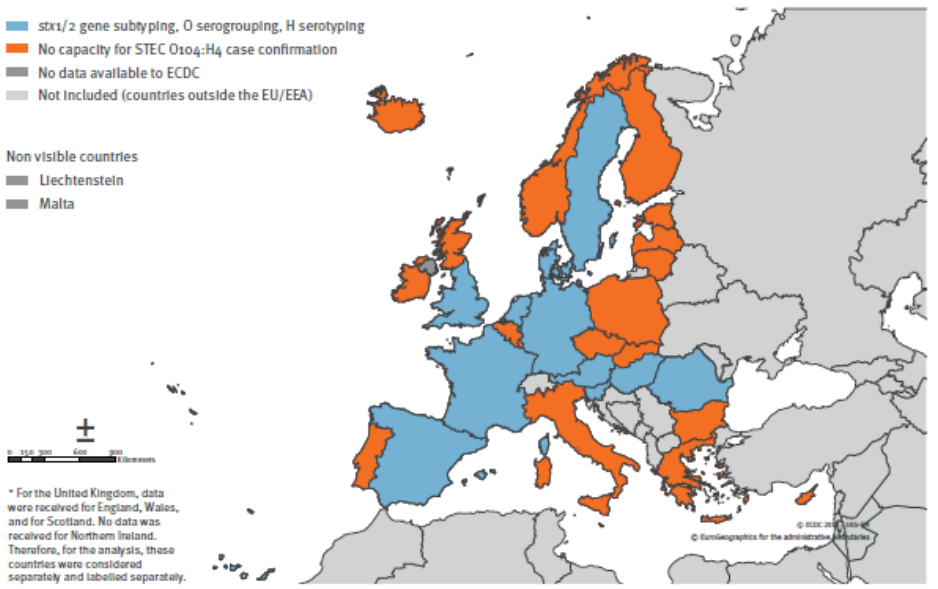
P Rosin (polyla.rosin@ecdc.europa.eu)[1], T Niskanen[2], D Palm[1], M Struelens[1], J Takkinen[2], Shiga toxin-producing Escherichia coli Experts of the European Union Food- and Waterborne Diseases and Zoonoses Network[3]
1. Microbiology Coordination section, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
2. Food and Waterborne Diseases and Zoonoses Programme, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
3. The STEC/VTEC experts of the Network, are listed at the end of this article

Citation style for this article:
Rosin P, Niskanen T, Palm D, Struelens M, Takkinen J, Shiga toxin-producing Escherichia coli Experts of the European Union Food- and Waterborne Diseases and Zoonoses Network. Laboratory preparedness for detection and monitoring of Shiga toxin 2-producing Escherichia coli O104:H4 in Europe and response to the 2011 outbreak. Euro Surveill. 2013;18(25):pii=20508. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20508

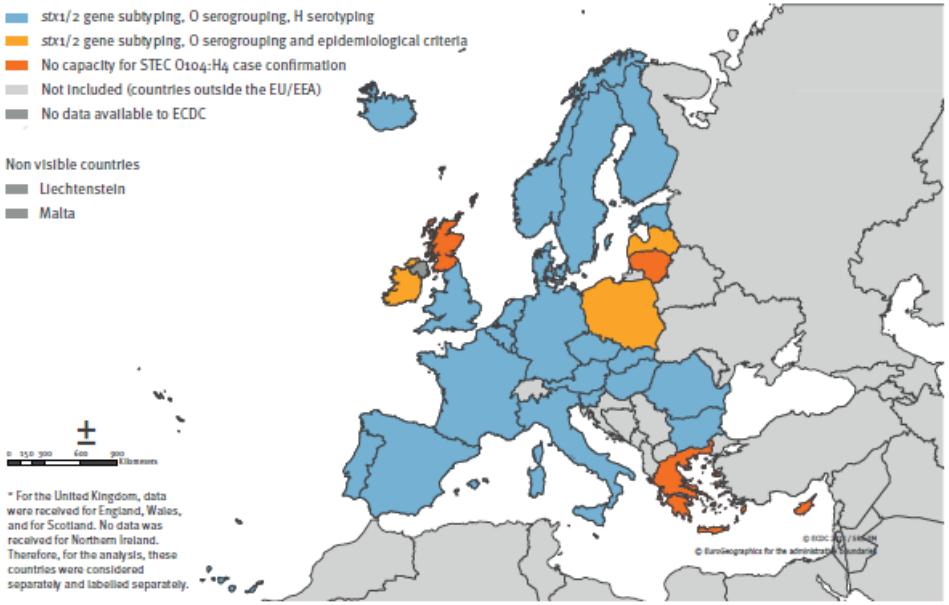
FIGURE 2

Capabilities of national reference laboratories in the European Union and European Economic Area for case detection and identification of Shiga toxin 2-producing *Escherichia coli* O104:H4 before and after the 2011 outbreak, March 2012

A: April 2011



B: December 2011



ECDC: European Centre for Disease Prevention and Control; EU/EEA: European Union/European Economic Area; STEC: Shiga toxin 2-producing *Escherichia coli*.

Laboratori nazionali riferimento

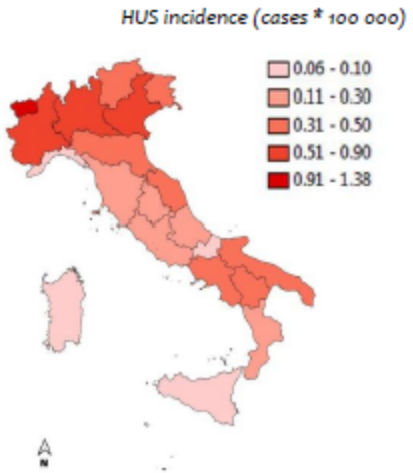
Sottotipizzazione genica Stx 1 / 2

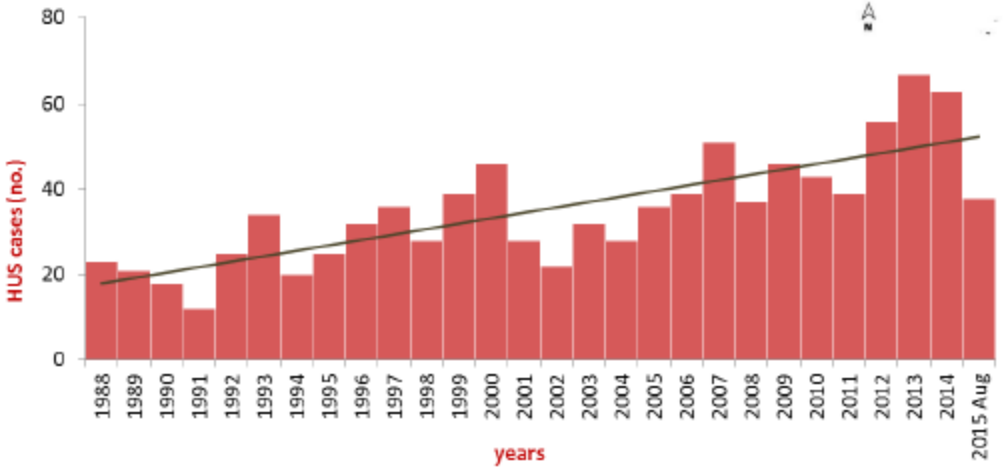
Sierologia per gruppo O

Sierotipizzazione H

Cases of HUS reported to the Italian Registry, by year, 1988-2015*

- Total HUS cases recorded: 984
- Cases with prodromal diarrhea: 85% (752/886)
- Mean HUS cases per year: 35,8 (range 12 – 67)
- Age (median): 26 months (range 0 - 15 yrs)
- Mean annual incidence rate:
  - 0.40 cases per 100,000 (0-15 yrs)
  - 1.17 cases per 100,000 (<4 yrs.) - RR=2.9

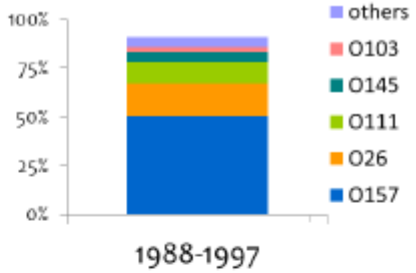


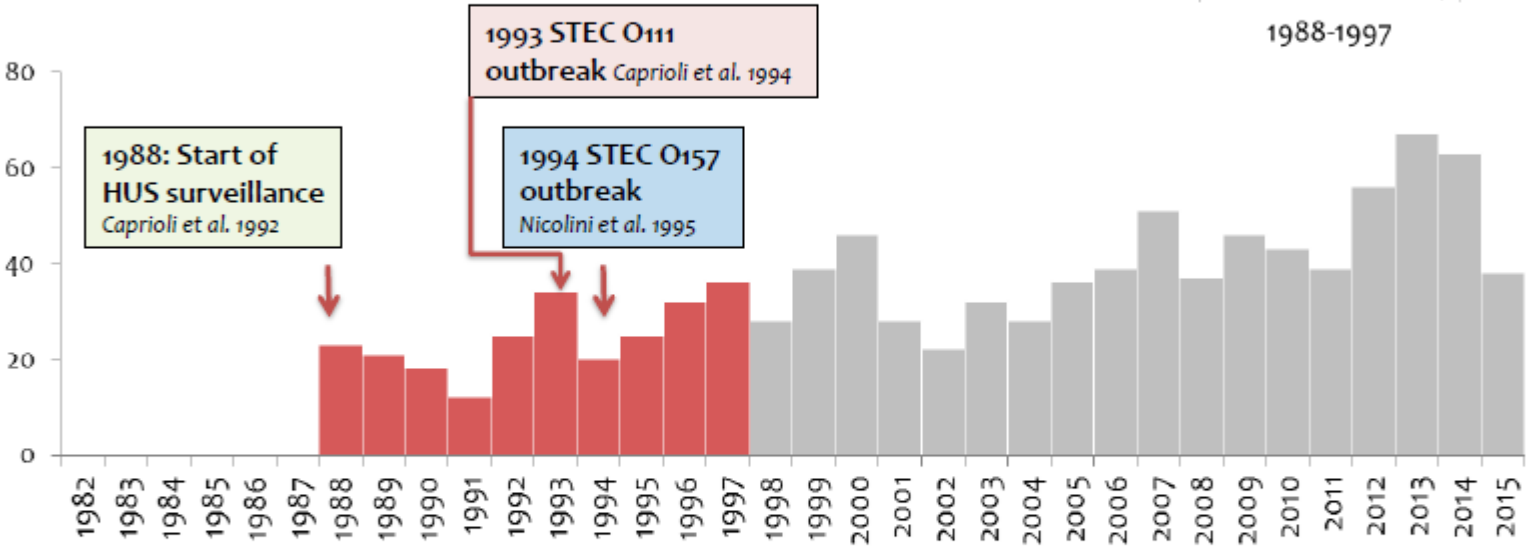


*Data updated as of 31 August 2015

Source of demographic data : ISTAT (www.istat.it)

1988 – 1997: STEC O157 is the most frequent serogroup





1993 STEC O111 outbreak *Caprioli et al. 1994*

1988: Start of HUS surveillance *Caprioli et al. 1992*

1994 STEC O157 outbreak *Nicolini et al. 1995*

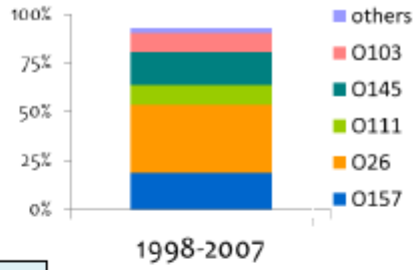
1983 STEC O157 is a leading cause of HUS *Karmali et al. 1983*

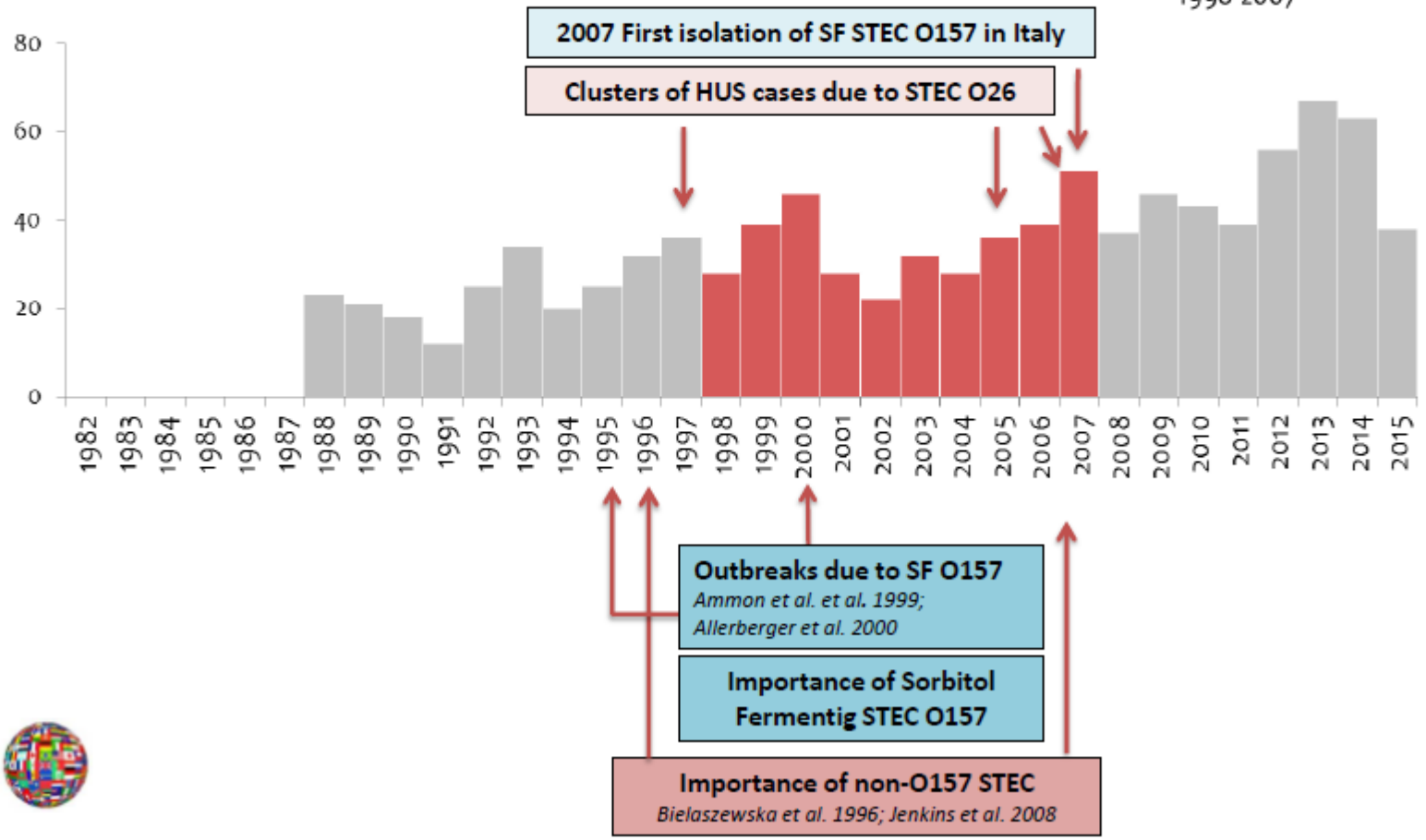
Large STEC O157 outbreaks *Riley et al. 1993; Michino et al. 1999*

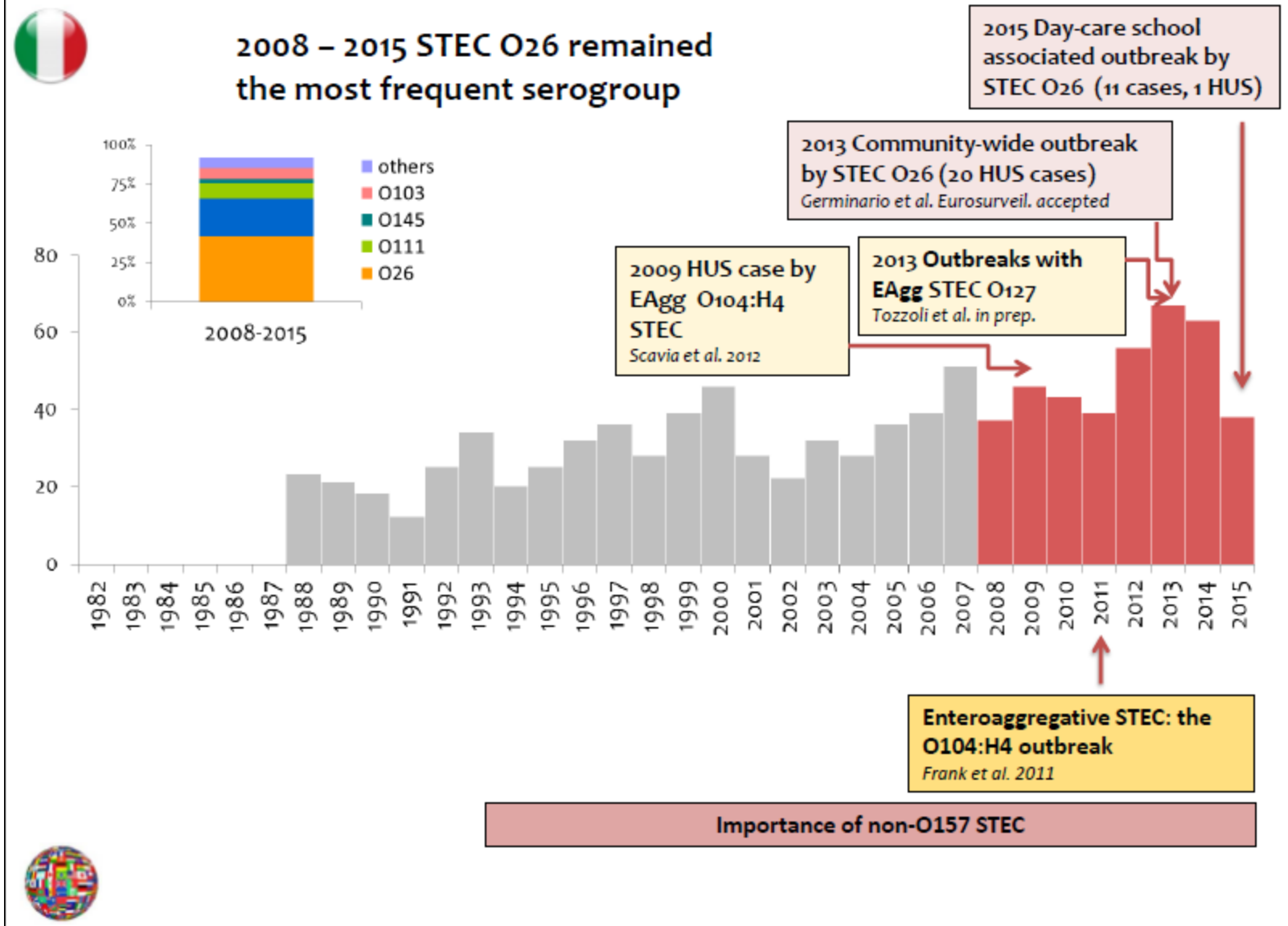
1995 HUS STEC O111 outbreak *MMWR 1995.*

1987 Cattle are reservoir of STEC O157 *Orskov et al. 1987*

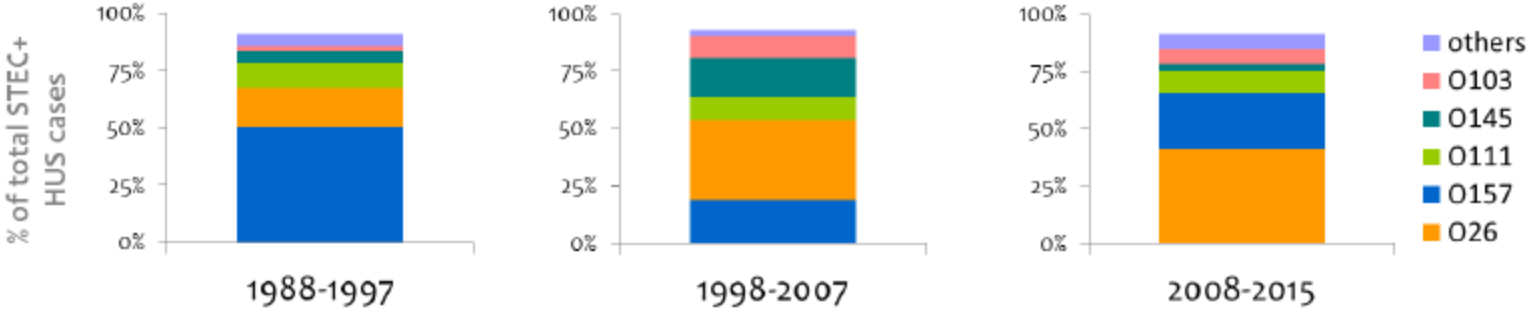
1998 – 2007: STEC O26 becomes the most frequent serogroup

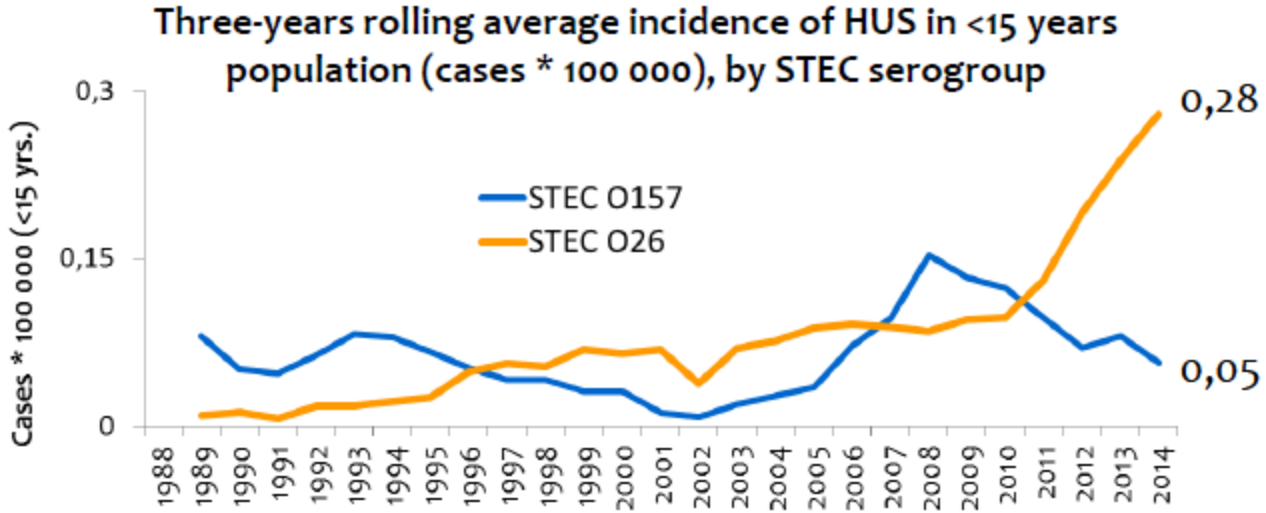





2008 – 2015 STEC O26 remained the most frequent serogroup
2015 Day-care school associated outbreak by STEC O26 (11 cases, 1 HUS)
2013 Community-wide outbreak by STEC O26 (20 HUS cases)
Germinario et al. Eurosurveil. accepted
2013 Outbreaks with EAgg STEC O127
Tozzoli et al. in prep.
2009 HUS case by EAgg O104:H4 STEC
Scavia et al. 2012
100%
75%
50%
25%
0%
2008-2015
others
O103
O145
O111
O026
80
60
40
20
0
1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
Enteroaggregative STEC: the O104:H4 outbreak
Frank et al. 2011
Importance of non-O157 STEC

HUS in Italy: the transition from STEC O157 to O26

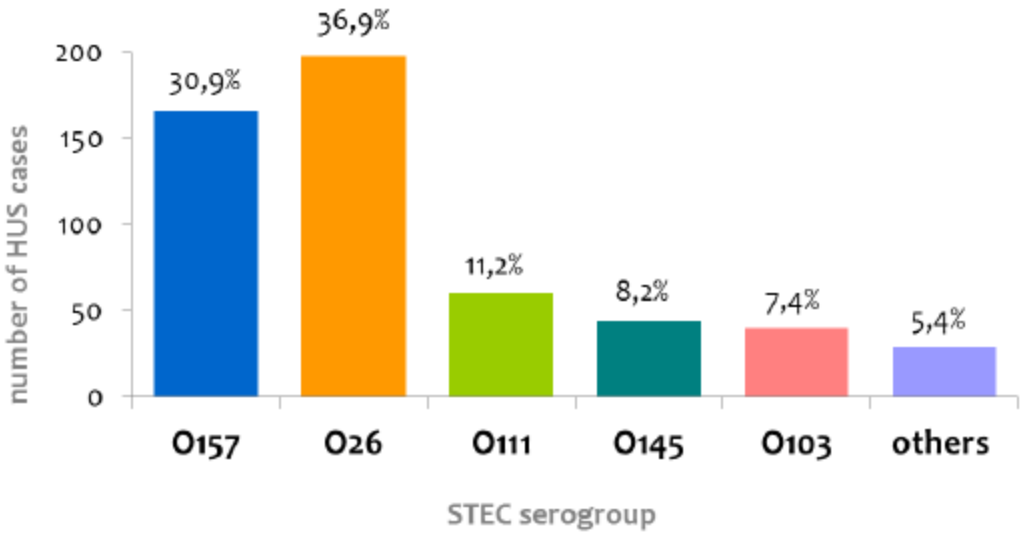




Source of data : ISTAT (www.istat.it) demographic

HUS and STEC infection in Italy

STEC serogroups most frequently detected 1988 – 2015*
(520 HUS cases*)



* 127 cases: STEC isolation; 393 cases: serological diagnosis

*Data updated as of 31 August 2015

World Health Organization

Emergencies preparedness, response

Enterohaemorrhagic *Escherischia coli* – United Kingdom

Disease outbreak news
20 July 2016

On 1 July 2016, the National IHR Focal Point for the United Kingdom notified WHO of an outbreak of Enterohaemorrhagic Shiga toxin-producing *Escherischia coli* (STEC) O157 PT34 in England and Wales.

The outbreak strain is not related to strains currently circulating amongst the UK bovine reservoir but rather closely related to sequences identified in people reporting recent travel to the Mediterranean region. This suggests that the outbreak strain is likely to be imported.

158 cases due to mixed salad leaves or blue cheese eating

Cases are predominantly female (75%) and over the age of 18 (91%) – the age range is between 1 and 98 years. Onset dates for cases range from 31 May 2016 to 5 July 2016.

Features of haemolytic uraemic syndrome (HUS) have been reported in seven cases. Two cases have died, both of whom have *E. coli* infection listed as a causative factor.

Stx-like
patogenesi

- Stx 1 e Stx 2 con omologia aminoacidica del 56%
- sub. A + sub. B (pentamero) ⟶ AB_5
- Secrezione nel lume intestinale da EHEC (*E. coli* enteroemorragici)
- Assorbimento
- ?? Trasporto sistemico via PMNL (Brigotti M; J. Clin. Microbiol 2006)
- Legame sub B con recettore glicolipidico di membrana Gb3 (cellule endoteliali glomerulari e epitelio tubulare) (nb affinità maggiore rispetto a PMNL !)
- Internalizzazione, inibizione sintesi proteica (sub. A)
- Apoptosi, necrosi ⟹ microangiopatia trombotica

NB: **Stx 2 più tossica. Maggiore adesività a Gb3 ! ! !**

Patogenesi alternative ?

Coinvolgimento complemento ?

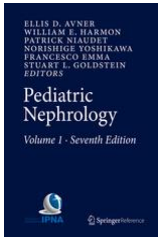
The Journal of Immunology

Shiga Toxin Activates Complement and Binds Factor H: Evidence for an Active Role of Complement in Hemolytic Uremic Syndrome

Dorothea Orth, Abdul Basit Khan, Asma Naim, Katharina Grif, Jens Brockmeyer, Helge Karch, Michael Joannidis, Simon J. Clark, Anthony J. Day, Sonja Fidanzi, Heribert Stoiber, Manfred P. Dierich, Lothar B. Zimmerhackl and Reinhard Würzner

J Immunol 2009; 182:6394-6400; ;

CFH gene mutation in a case of Shiga toxin-associated hemolytic uremic syndrome (STEC-HUS)



Caroline Caillaud [1] · Ariane Zaloszyc [1] · Christoph Licht [2] · Valérie Pichault [3] · Véronique Frémeaux-Bacchi [4] · Michel Fischbach [1]

Pediatr Nephrol (2016) 31:157–161

Stx-like HUS
decorso clinico

Forme epidemiche (tossinfezione alimentare) e forme sporadiche
Predilezione generale < 10 aa di età ma

in Germania (O 104:H4) età adulta (88%, età media 44 aa) !!!
In Gran Bretagna (2016: O 157) età adulta, sesso F

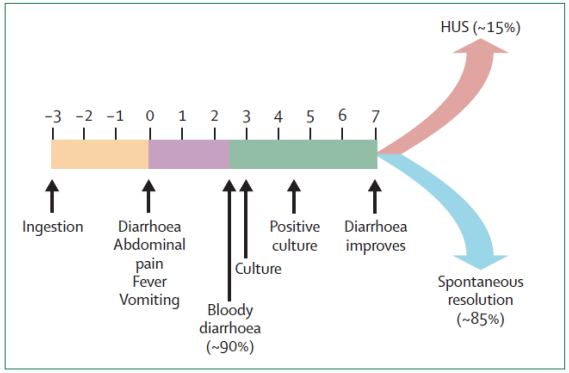


Figure 3: Progression of *E coli* O157:H7 infections in children

- Incubazione 2-12 gg
- Febbre caratteristica non usuale !! (dd con salmonellosi)
- Dolori addominali intensi, diarrea ± nausea e vomito
- Progressione a diarrea emorragica in 1-2 gg
- **Evoluzione in HUS in 7-10 gg (trombocitopenia primo sintomo)**
- Complicanze HUS: Insufficienza renale, Stroke, Convulsioni, Coma, Emorragie.
  Ipertensione arteriosa 15-20% dopo 3 aa

Possibile infezione da STEC

Criteri e management

- Diarrea **+ intensi dolori addominali**
  No febbre
- Diarrea emorragica ⟹
- ⟹ reidratazione con cristalloidi ev

- No antibioticoterapia per rischio di progressione HUS ???

  (Wong CS N Engl J Med 2000. Dundas S CID 2001 .Launders N BMJ Open 2016)

- No farmaci anti motilità

Stx-like HUS

management

- Evoluzione verso HUS

  1) trombocitopenia
  2) emolisi
  3) insufficienza renale

- Rischio di sviluppo HUS per ~ 1 settimana fino a risalita Plt

Identificazione tossina Shiga e EHEC

- L'accurata, rapida identificazione di STEC è fondamentale per la gestione del paziente

- Confermare STEC come eziologia della TMA
  - Identificazione nelle feci della tossina Shiga o EHEC
  - IgG o IgM anti EHEC nel siero

- In grandi coorti di pazienti la tossina Shiga o EHEC possono essere identificate nella maggior parte dei pazienti
  - Nel 79% di 619 pazienti considerati affetti da STEC-HUS era stata identificata EHEC

1.Petruzziello-Pellegrini TN et al. *Curr Opin Nephrol Hypertens.* 2012;21:433-440.
2.Rosales A et al. Presented at: American Society of Nephrology Annual Meeting; November 10, 2011. Abstract TH-PO052.

Diagnosi

- Coprocoltura per *EHEC*
- Ricerca tossina libera nelle feci (metodi immunocromatografici, PCR)
- (cultura, cromatografia per Stx a PG)

- Istituto Superiore Sanità

  Ricerca nel siero di IgG e IgM per :

  E. coli O 26 ; O 157; O 111; O 103; O 121; O 145.

aHUS e infezioni

aHUS (10-15%) Stx neg

familiare ⇄ sporadiche

(anomalie complemento)
FH, FI, CD46, ...

→ ....

infezioni come *trigger*

infezioni
(40 % *S. pneumoniae*)
(Sp-HUS)

Atypical Hemolytic Uremic Syndrome

David Kavanagh, MD, PhD, Tim H. Goodship, MD,* and Anna Richards, MD, PhD†*

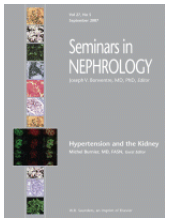


Table 1. Triggers of aHUS

Infective triggers	Reference
Non-Stx toxin diarrheal illnesses	51,94,95
Norovirus	161,162
Campylobacter upsaliensis	163
Clostridium difficile	164
Respiratory infections	51
Bordetella pertussis infection	10,165
Streptococcus pneumonia	166
Haemophilus influenzae	10
Other bacterial	
Fusobacterium necrophorum	167
Viral illnesses	
Varicella	168
Cytomegalovirus	169
Influenza H1N1	170
Hepatitis A	171
Hepatitis C	172
Human immunodeficiency virus	173
Coxsackie B virus	174
Epstein–Barr virus	175
Dengue	176
HHV6	177
Human parvovirus B19	178
Parasites	
Plasmodium falciparum	179

Seminars in Nephrology, Vol 33, No 6, November 2013, pp 508–530

Varicella as a trigger of atypical haemolytic uraemic syndrome associated with complement dysfunction: two cases

Theresa Kwon[1], Alexandre Belot[2], Bruno Ranchin[2], Véronique Baudouin[1], Véronique Fremeaux-Bacchi[3], Marie-Agnès Dragon-Durey[3], Pierre Cochat[2] and Chantal Loirat[1]

Case reports

A 5-year-old boy [patient 1

. MCP expression on the granulocyte surface was below the normal range and a heterozygous C30 F mutation in *MCP* exon 2 (c.191G >T) was demonstrated

A 4-year-old girl [patient 2

Four relapses within 5 months

Ten years after onset, C3, C4, CFB, CFH and CFI levels were normal, but anti-CFH antibodies and a deletion of CFH-related genes *CFHR1-CFHR3* were demonstrated. No mutations of *CFH*, *CFI* or *MCP* were found

Nephrol Dial Transplant (2009) 24: 2752–2754

Dengue Fever–Induced Hemolytic Uremic Syndrome

To the Editor—Dengue virus infection

Clinical Infectious Diseases 2006; 43:800–801

SciMedCentral Journal of Clinical Nephrology and Research

Case Report

Haemolytic Uraemic Syndrome Associated with Dengue Viral Infection

Wan Rohaslizan WD[1], Rizawati RI[1], Shamila K[1], Shafira MS[2], Lydia K[1] and Ruslinda M[1]*

*Corresponding author
Ruslinda Mustafar, Consultant Physician and Nephrologist, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Jalan Yaacob Latiff, 56000 Cheras, Kuala Lumpur, Malaysia, Tel: 6019-2140859, 603-91456086; Email: ruslinda.m@gmail.com

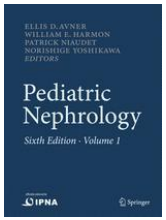
Submitted: 29 March 2016
Accepted: 15 April 2016
Published: 16 April 2016
ISSN: 2379-0652

Incomplete penetrance of *CD46* mutation causing familial atypical hemolytic uremic syndrome

Divya Bhatia[1] · Priyanka Khandelwal[1] · Aditi Sinha[1] · Pankaj Hari[1] · Hae Il Cheong[2,3,4] · Arvind Bagga[1]

Results Three siblings, two of whom were symptomatic, had markedly decreased (<10 %) cell surface expression of CD46 and homozygous splice site mutation (IVS2+2 T>G) in the *CD46* gene; the other 10-year-old sibling was asymptomatic.

The illness was preceded by dengue shock syndrome in the index case. Both parents and two other siblings were heterozygous for this *CD46* mutation.



Pandemic H1N1 influenza A infection and (atypical) HUS—more than just another trigger?

Upton Allen · Christoph Licht

context, reports on the development of (a)HUS in patients concomitantly diagnosed with pandemic H1N1 influenza A (pH1N1) infection are of great interest. They establish—for the first time in the literature—the link between aHUS and pH1N1 infection. While illnesses associated with pH1N1

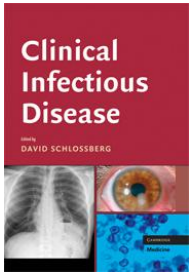
Pediatr Nephrol (2011) 26:3–5

HIV e microangiopatia trombotica

Un capitolo da scrivere

Frequency and Significance of HIV Infection among Patients Diagnosed with Thrombotic Thrombocytopenic Purpura

Melody Benjamin,[1] Deirdra R. Terrell,[1,2] Sara K. Vesely,[2] Gene W. Voskuhl,[3] Bruce J. Dezube,[4] Johanna A. Kremer Hovinga,[5] Bernhard Lämmle,[5] and James N. George[1,2]



characteristic clinical features of TTP, microangiopathic hemolytic anemia, thrombocytopenia, and abnormal renal function, were manifestations of advanced HIV infection [10]. These different perspectives reflect the

Conclusions. HIV infection, similar to other inflammatory conditions, may trigger acute episodes of TTP in susceptible patients. More commonly, acquired immunodeficiency syndrome–related disorders may mimic the clinical features of TTP. If the diagnosis of TTP is suggested in a patient with HIV infection, there should be careful evaluation for alternative diagnoses and cautious consideration of plasma exchange, the required treatment for TTP.

Clinical Infectious Diseases 2009; 48:1129–37

EXCEPTIONAL CASE

Thrombotic microangiopathy and human immunodeficiency virus in the era of eculizumab

Anna Jin[1,2], Laleh Boroujerdi-Rad[1,2], Gaurang Shah[1,2] and Joline L.T. Chen[1,2]

We present a case of a patient with human immunodeficiency virus infection who developed TMA and was successfully treated with eculizumab. The effect of long-term treatment with this new medication is unknown, and further studies are needed to

Clinical Kidney Journal, 2016, 1–4

Sarmiento et al. Journal of Medical Case Reports (2016) 10:152
DOI 10.1186/s13256-016-0938-z

Journal of
Medical Case Reports

CASE REPORT Open Access

Thrombotic microangiopathy as first manifestation of acute human immunodeficiency virus infection: a case report and review of the literature

M. Sarmiento[1*], M. E. Balcells[2] and P. Ramirez[1]

Journal of Medical
Case Reports

Laboratory tests showed lymphopenia, anemia, severe thrombocytopenia, acute renal failure, lactate dehydrogenase (LDH) twice over normal value, and hyperbilirubinemia that progressively worsened during the first week of hospitalization (Table 1).

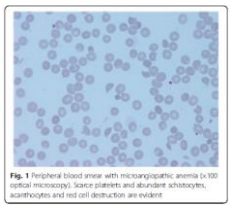


Fig. 1 Peripheral blood smear with microangiopathic anemia (x100 optical microscopy). Scarce platelets and abundant schistocytes, acanthocytes and red cell destruction are evident

Clinical Kidney Journal, 2016, vol. 9, no. 4, 576–579

a-HUS da *S. pneumoniae*

Sp-HUS

a-HUS

Sp-HUS

- 5 % di HUS nei bambini in U.S.
- 40 % di a-HUS non familiari
- Prevalenza in bambini < 2aa; rara negli adulti
- Manifestazioni cliniche 7-9 gg dopo inizio con meningite, polmonite (range 3-13)
- Malattia più severa !!! Maggiore letalità, maggior ricorso emodialisi, maggiori sequele a lungo termine (mortalità 2-12% ; insufficienza renale 10 - 16%).
- Complicanze extra-renali (pancreatiti, cardiopatie, trombosi..)
- Terapia antibiotica necessaria !

- NB: dd ardua con CID

a-HUS da *S.pneumoniae* patogenesi 1

- a) *S. pneumoniae* libera N-acetyl neuraminidasi
- b) esposizione antigene Thomsen-Friedereich su GR, Plt, e glomeruli per rottura di acido sialico in cui è nascosto
- c) Riconoscimento antigene da IgM naturali ? (agglutinine fredde) con poliagglutinazione, emolisi e microangiopatia trombotica.

??? Utilità Plasmaferesi ????

Red blood cell Thomsen-Friedenreich antigen expression and galectin-3 plasma concentrations in *Streptococcus pneumoniae*–associated hemolytic uremic syndrome and hemolytic anemia

The results obtained on RBCs from P-HUS patients and on control RBCs treated with various concentrations of neuraminidase suggest that differences in neuraminidase activity among P-HUS patients are as high as 100-fold.

TRANSFUSION 2015;55:1563–1571

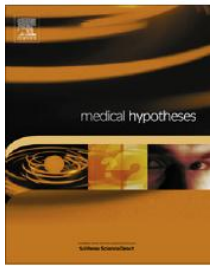
a-HUS da *S. pneumoniae* patogenesi 2

- a) *S. pneumoniae* libera N-acetyl neuraminidasi
- b) lesione dei siti di legame a base di acido sialico del Fattore H
- c) impossibilità ad inibire legame fattore B a convertasi
- d) attivazione C3 convertasi e C5 convertasi

Utilità Eculizumab !!!

Does dysregulated complement activation contribute to haemolytic uraemic syndrome secondary to *Streptococcus pneumoniae*?

Rodney D. Gilbert *, Arvind Nagra, Mushfequr R. Haq



A B S T R A C T

but there was an apparent improvement in her condition after administration of eculizumab. The most widely accepted mechanism for pneumococcal HUS is endothelial cell damage by pre-formed antibodies against the Thomsen–Friedenreich antigen. This explanation does not bear rigorous scrutiny. We postulate that transiently dysregulated complement activation may play a role in the pathogenesis of pneumococcal disease. We further postulate that the mechanism could be enhanced binding of factor H to the neuraminidase-altered surface of endothelial cells or reduced binding of factor H to the endothelial cell surface mediated by competitive binding of factor H by pneumococcal surface protein C (pspC).

Medical Hypotheses 81 (2013) 400–403

TTP

Thrombotic thrombocytopenic purpura

CONGENITA

ACQUISITA

Inibitori autoimmuni
ADAMTS 13

Infezioni

Transfusion. 2010 January ; 50(1): 208–212. doi:10.1111/j.1537-2995.2009.02391.x.

A novel association of acquired ADAMTS13 inhibitor and acute dengue virus infection

Fernanda C. Rossi, **Rodrigo N. Angerami**, **Erich V. de Paula**, **Fernanda L. Orsi**, **Dezhi Shang**, **Vânia M. del Guercio**, **Mariângela R. Resende**, **Joyce M. Annichino-Bizzacchi**, **Luiz J. da Silva**, **X. Long Zheng**, and **Vagner Castro**
Hematology and Hemotherapy Center and the Department of Medicine, Medical Sciences

CASE REPORT—Here we provide the first evidence of a case of antibody formation against ADAMTS13 (ADAMTS13 inhibitor) in the course of a severe acute DV infection resulting in thrombotic microangiopathy (TMA). The patient presented with classical dengue symptoms (positive epidemiology, high fever, myalgia, predominantly in the lower limbs and lumbar region for 1 week) and, after 11 days of initial symptoms, developed TMA. Clinical and laboratorial investigation of dengue and TMA was performed.

RESULTS—The patient presented with ADAMTS13 inhibitor (IgG) during the acute phase of the disease, without anti-platelet antibodies detectable. Dengue infection had laboratorial confirmation. There were excellent clinical and laboratory responses to 11 serial plasma exchanges. Anti-ADAMTS13 inhibitor disappeared after remission of TMA and dengue resolution. No recurrence of TMA symptoms was observed after 2-year follow-up.

OPEN ACCESS Freely available online

PLoS PATHOGENS

Severe *Plasmodium falciparum* Malaria Is Associated with Circulating Ultra-Large von Willebrand Multimers and ADAMTS13 Inhibition

Deirdre Larkin[1], Bas de Laat[2], P. Vince Jenkins[1], James Bunn[3,4], Alister G. Craig[4], Virginie Terraube[1], Roger J. S. Preston[1], Cynthia Donkor[4,5], George E. Grau[6], Jan A. van Mourik[2], James S. O'Donnell[1,7]*

http://crim.sciedupress.com Case Reports in Internal Medicine 2016, Vol. 3, No. 3

CASE REPORTS

Thrombotic thrombocytopenic purpura associated with *Klebsiella* pneumonia in the background of alcoholic liver cirrhosis

Satoshi Ichikawa*[1,2], Keiju Sasaki[1], Taro Takahashi[2], Masaki Hayakawa[3], Masanori Matsumoto[3], Hideo Harigae[1]

INTERNAL MEDICINE

□ CASE REPORT □

Influenza A Infection Triggers Thrombotic Thrombocytopenic Purpura by Producing the Anti-ADAMTS13 IgG Inhibitor

Nobuharu Kosugi [1], Yuya Tsurutani [1], Ayami Isonishi [2], Yuji Hori [2], Masanori Matsumoto [2] and Yoshihiro Fujimura [2]

http://crim.sciedupress.com Case Reports in Internal Medicine 2016, Vol. 3, No. 3

CASE REPORTS

Thrombotic thrombocytopenic purpura associated with *Klebsiella* pneumonia in the background of alcoholic liver cirrhosis

Satoshi Ichikawa*[1,2], Keiju Sasaki[1], Taro Takahashi[2], Masaki Hayakawa[3], Masanori Matsumoto[3], Hideo Harigae[1]

Medicine

OBSERVATIONAL STUDY

OPEN

Decreased ADAMTS 13 Activity is Associated With Disease Severity and Outcome in Pediatric Severe Sepsis

Jainn-Jim Lin, MD, Oi-Wa Chan, MD, Hsiang-Ju Hsiao, MD, Yu Wang, MD, Shao-Hsuan Hsia, MD, and Cheng-Hsun Chiu, MD, PhD

Karim *et al. BMC Pediatrics* 2013, **13**:44
http://www.biomedcentral.com/1471-2431/13/44

BMC Pediatrics

RESEARCH ARTICLE Open Access

Deficiency of ADAMTS-13 in pediatric patients with severe sepsis and impact on in-hospital mortality

Farheen Karim[1*], Salman Naseem Adil[1], Bushra Afaq[1] and Anwar ul Haq[2]

ADAMTS13 activity and the presence of acquired inhibitors in human immunodeficiency virus–related thrombotic thrombocytopenic purpura

Karen Gunther, Dominique Garizio, and Paul Nesara

RESULTS: The patients fell clearly into two groups with regard to ADAMTS13 activity. Six patients (30%) had activity within the normal range, whereas the remaining 14 patients had severely reduced levels. Of the patients with reduced activity, only 5 patients had a detectable inhibitor whereas 8 showed no evidence of an inhibitor. There was significant correlation between normal ADAMTS13 activity and lower CD4 counts ($p = 0.049$).

CONCLUSION: The heterogeneity with regard to ADAMTS13 activity and the absence of inhibitors in the majority of patients indicate that other factors are important in the pathogenesis of HIV-related TTP. VWF release and localized coagulation activation due to direct viral or cytokine-mediated endothelial cell injury is likely to be playing a major role.

TRANSFUSION 2007;47:1710-1716.

Hemorrhagic Stroke in an Adolescent Female with HIV-Associated Thrombotic Thrombocytopenic Purpura

Natella Rakhmanina[1,4,*], **Edward CC Wong**[2,4,5], **Jeremiah C Davis**[6], and **Patricio E Ray**[3,4]

diagnosis and treatments for HIV-ITP and HIV-TTP were considered simultaneously. A decrease in plasma ADAMTS13 activity (<5%) without detectable inhibitory antibodies confirmed the diagnosis of HIV-TTP. Re-initiation of ART and plasma exchange resulted in a marked decrease

J AIDS Clin Res. ; 5(6): . doi:10.4172/2155-6113.1000311.

Conclusioni

- Patologia con necessità di approfondimenti ulteriori in senso patogenetico
- Implicazioni terapeutiche rispetto alla patogenesi
- Sfida nella comprensione dei meccanismi di trigger infettivo nelle aHUS e TTP

E ora … affrontiamo le sfide

Grazie dell’attenzione

0021326-21/07/2016-DGPRE-DGPRE-P

Ministero della Salute

DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA
UFFICIO 5 PREVENZIONE DELLE MALATTIE TRASMISSIBILI E PROFILASSI INTERNAZIONALE

A

OGGETTO: *ESCHERICHIA COLI* ENTEROEMORRAGICO NEL REGNO UNITO

20 luglio 2016

Il 1° luglio 2016, il punto di contatto nazionale per il RSI del Regno Unito ha notificato all'OMS un'epidemia di *Escherichia coli* produttore di shiga tossina enteroemorragica (STEC) O157 PT34 in Inghilterra e Galles.

Alla data del 14 luglio, sono stati identificati 158 casi, 105 dei quali sono stati classificati come casi confermati e 53 come probabili. Quattro di questi pazienti sono ancora ospedalizzati. In sette casi sono state segnalate caratteristiche di sindrome uremico emolitica (HUS). Due casi sono deceduti, e in entrambi i casi l'infezione da *E. coli* è stata indicate come causa di morte.

I casi sono distribuiti su tutto il territorio del Regno Unito, ma la maggior parte (91%) risiede in Inghilterra. L'epidemia è caratterizzata da piccoli cluster multipli legati alla ristorazione e alle strutture di assistenza residenziale. Il tasso di ospedalizzazione è alto (40%). I casi sono prevalentemente di sesso femminile (75%) e di età superiore a 18 anni (91%) – l'intervallo d'età varia fra 1 e 98 anni. Le date di insorgenza della sintomatologia sono comprese fra il 31 maggio 2016 e il 5 luglio 2016.