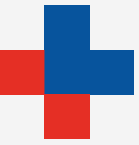


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**REGIONE  
LAZIO**



**SAPIENZA  
UNIVERSITÀ DI ROMA**

**Malattie dell'Apparato Digerente e del Fegato  
Sapienza Università di Roma**

**Diarrea cronica in pz con  
multiple comorbidità**

**Dott.ssa Chiara Petraroli**

**Roma, 13 Gennaio 2018**

## CASO CLINICO

- Donna, 80 anni. H 1,80 m; P 70 kg (BMI 21,6)
- **Visita ambulatoriale ad Ottobre u.s**
  - Diarrea (max 10 evacuazioni di feci liquide, senza sangue nè muco) da circa 3-4 settimane
  - Febbre (fino a 38°C)
  - Dolore addominale nei quadranti bassi dell'addome di lieve intensità

## Anamnesi patologica remota

Pancreatite cronica diagnosticata nel 2016

- [Insufficienza pancreatica esocrina \(elastasi < 15 mcg/g di feci\)](#)
- [Diabete IIIc](#)

Leucemia linfatica cronica dal 2003

- pregresso episodio di riattivazione CMV e VZV

Ipotiroidismo

Diverticolosi colica

## Terapia

Creon 10000 U 2 + 4 + 4 cp

Novonorm 1 mg + 2 mg

Pantorc 40 mg 1 cp

Betmiga 50 mg 1 cp

Cymbalta 30 mg 1 cp

Cardicor 1,25 mg 1 cp

Eutirox 75 mcg

Immunoglobuline ev (a cicli)

Aciclovir 400 mg

Bactrim 160 + 800 mg

Ursobil HT 450 mg

Frequenza

Comune

Comune

Comune

Comune

Comune

Rara

Comune

# Insufficienza pancreatica esocrina

- PEI refers to an insufficient secretion of pancreatic enzymes (acinar function) and/or sodium bicarbonate (ductal function).
  - Due to the large reserve capacity of the pancreas, 'mild' to 'moderate' exocrine insufficiency can be compensated, and overt steatorrhea is not expected unless the secretion of pancreatic lipase is reduced to <10% of normal ('severe'/'decompensated' insufficiency).
  - However, patients with 'compensated' PEI also have an increased risk of nutritional deficiencies (in particular, of lipid-soluble vitamins with respective clinical consequences).

# Diabete mellito

Altered motility  
(increased or  
decreased)

Associated  
diseases

Drugs (especially  
acarbose,  
metformin)

SIBO

Schiller LR, Pardi DS, Sellin JH. Chronic Diarrhea: Diagnosis and Management. Clin Gastroenterol Hepatol. 2017 Feb;15(2):182-193.e3.

# Leucemia Linfatica Cronica

- Chronic lymphocytic leukemia (CLL) is a malignancy characterized by the progressive accumulation of mature B lymphocytes in the peripheral blood, bone marrow and lymphoid tissues.

Tadmor T, Welslau M, Hus I. A review of the infection pathogenesis and prophylaxis recommendations in patients with chronic lymphocytic leukemia. *Expert Rev Hematol.* 2018 Jan;11(1):57-70.

Downloaded by [University of New England] at 01:40 22 November 2017

Table I: Intrinsic CLL-related immune dysregulation

<b>B-cell dysfunction</b>	<ul style="list-style-type: none"><li>• Hypogammaglobulinemia (IgG3 and IgG4 particularly affected) [4, 22]</li><li>• Poor antigen presentation [4]</li><li>• B-cell regulatory activity by CLL cells [28, 125]</li><li>• B-cell anergy [4]</li></ul>
<b>T-cell dysfunction</b>	<ul style="list-style-type: none"><li>• Decrease response to mitogens [25]</li><li>• Increase T-cell exhaustion makers [23]</li><li>• Impaired Immunological T-cell Synapsis [23]</li><li>• Inversion of CD4+/CD8+ ratio [23]</li><li>• High regulatory T cell number [27]</li><li>• Aberrant cellular cross talk [126]</li></ul>
<b>Cytokines levels</b>	<ul style="list-style-type: none"><li>• Overexpression of IL-10 [127] and transforming growth factor b [128]</li><li>• IL-2 downregulation [25]</li></ul>
<b>Complement</b>	<ul style="list-style-type: none"><li>• Decreased levels (especially of properdin) [129]</li><li>• Defects in complement function (activation and binding) [129]</li></ul>
<b>Neutrophil and phagocytic function</b>	<ul style="list-style-type: none"><li>• Reduced neutrophil count [35]</li><li>• Defects in neutrophil phagocytic and bactericidal activity [130]</li><li>• Deficient granules (lysozyme, b-glucuronidase myeloperoxidase) [29]</li><li>• Abnormal chemotaxis [130]</li></ul>
<b>Other</b>	<ul style="list-style-type: none"><li>• Defects in monocytes function and enzyme levels [35]</li></ul>

CLL, chronic lymphocytic leukemia; FC, fludarabine + cyclophosphamide; FCR, fludarabine + cyclophosphamide + rituximab; IgG, immunoglobulin; IL, interleukin.



# Historical Features to Consider in Patients Presenting with Diarrhea

Duration: acute (<4 weeks) vs. chronic (≥4 weeks)

Onset: congenital, abrupt, gradual

Pattern: continuous, intermittent

Epidemiology

Iatrogenic factors: drugs, radiation, surgery

Systemic diseases: endocrine, collagen vascular, neoplastic, immunologic

Stool appearance: watery, bloody, fatty

Fecal incontinence: present, absent

Abdominal pain: location, relation to meals or bowel movements, aggravating and relieving factors

Weight loss

Aggravating factors: diet, stress

Alleviating factors: diet, over-the-counter drugs, prescription drugs

## Supplementary Table 2. Epidemiologic Associations and Patient Characteristics<sup>6</sup>

### Travelers

- Bacterial infection (mostly acute)
- Protozoal infections (eg, amebiasis, giardiasis)
- Tropical sprue
- Epidemics and outbreaks
- Bacterial infection
- Epidemic idiopathic secretory diarrhea (eg, Brainerd diarrhea)
- Protozoal infection (eg, cryptosporidiosis)
- Viral infection (eg, rotavirus)
- Diabetic patients
- Altered motility (increased or decreased)
- Associated diseases
  - CD
  - Pancreatic exocrine insufficiency
  - SIBO
- Drugs (especially acarbose, metformin)
- Patients with acquired immunodeficiency syndrome
  - Drug side effects
  - Lymphoma
- Opportunistic infections (eg, cryptosporidiosis, cytomegalovirus, herpesvirus, *Mycobacterium avium* complex)
- Institutionalized and hospitalized patients
  - Clostridium difficile* infection
  - Drug side effects
  - Fecal impaction with overflow diarrhea
  - Ischemic colitis
  - Tube feeding



# Cause di diarrea cronica

- Watery diarrhea
  - Osmotic diarrhea
    - Carbohydrate malabsorption
    - Osmotic laxatives (eg, Mg<sup>2+</sup>, PO<sub>4</sub><sup>-3</sup>, SO<sub>4</sub><sup>-2</sup>)
  - Secretory diarrhea
    - Bacterial toxins
    - Bile acid malabsorption
    - IBD (some cases)
      - Crohn's disease
    - Microscopic colitis
      - Collagenous colitis
      - Lymphocytic colitis
    - Medications and toxins
    - Disordered motility
      - Diabetic autonomic neuropathy
      - IBS
      - Postsympathectomy diarrhea
      - Postvagotomy diarrhea
  - Endocrinopathies
    - Addison's disease
    - Neuroendocrine tumors
    - Hyperthyroidism
    - Mastocytosis
    - Medullary carcinoma of the thyroid
  - Idiopathic secretory diarrhea (epidemic and sporadic)
  - Stimulant laxative abuse
  - Neoplasia
    - Colon carcinoma
    - Lymphoma
    - Villous adenoma
  - Vasculitis
- Inflammatory diarrhea
  - Diverticulitis
  - Infectious diseases
  - Invasive bacterial infections (eg, tuberculosis, yersinosis)
  - Invasive parasitic infections (eg, amebiasis, strongyloidiasis)
  - Pseudomembranous colitis
  - Ulcerating viral infections (eg, cytomegalovirus, herpes simplex virus)
  - IBD (most cases)
    - Crohn's disease
    - Ulcerative colitis
    - Ulcerative jejunoileitis
  - Microscopic colitis (some cases)
  - Ischemic colitis
  - Neoplasia
    - Colon cancer
    - Lymphoma
  - Radiation colitis
- Fatty diarrhea
  - Malabsorption syndromes
    - Mesenteric ischemia
    - Mucosal diseases (eg, CD, Whipple's disease)
    - SBS
    - SIBO
  - Maldigestion
    - Inadequate luminal bile acid concentration
    - Pancreatic exocrine insufficiency

# Diarrea infettiva?

Ricerca tossina C.  
difficile

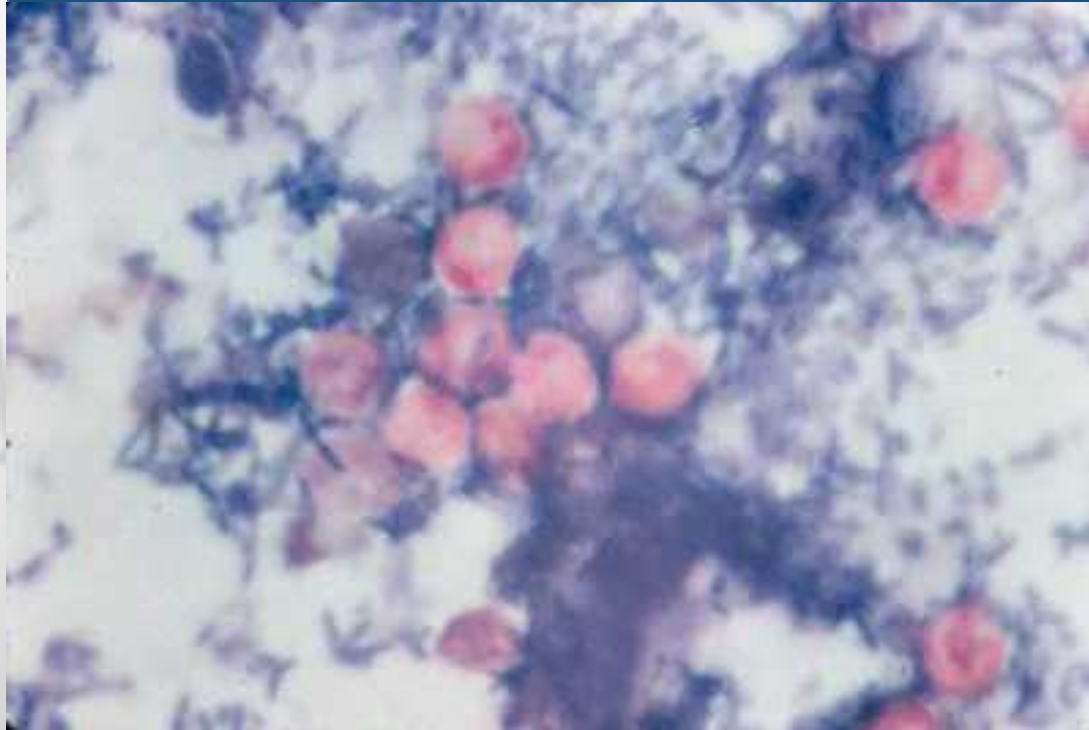
- Negativa

Esame colturale delle  
feci per germi comuni

- Negativo

Esame parassitologico delle feci su singolo campione

- POSITIVO, presenza di oocisti di *Cryptosporidium spp*
  - *Impostata tp con Metronidazolo 250 mg 2 cp q8h*



Diarrea da  
farmaci/colite  
microscopica?

1

Sospensione  
Aciclovir,  
Bactrim, Ursobil  
e Pantorc

2

Terapia con  
Intesticort 3  
mg/tid

- Persistenza della sintomatologia
- Calo ponderale di circa 6 kg
- Ipokaliemia grave (2.6 mmol/l)



Accesso in DH



- **Ricerca C. difficile tossigenico** (tossina + antigene GDH)
  - Negativo
- **Coprocoltura Salmonella/Shigella/Campylobacter**
- **Parassitologico** su singolo campione
- **Rettosigmoidoscopia**
  - Esame condotto fino a circa 40 cm dal margine anale. Eseguite biopsie.

---

Gennaio u.s.



- Parametri vitali

PA	T°	FC	SpO <sub>2</sub>
115/70	37,7 °C	74 bpm	94%

- Esami ematochimici

GR (4,4-10,6 10 <sup>6</sup> /uL)	Hb (13,0-18,0 g/dl)	Hct (42-52%)	MCV (85-98 fl)	GB (4,3-10,8 10 <sup>3</sup> /uL)	L (16-45%)	PCR (0-0,5 mg/dl)	K+ (3,5- 5,5 mmol/l)
3,0	10,5	32	<b>106</b>	4930	66,8	<b>2,86</b>	<b>2.2</b>

- Terapia

- Antibiotica empirica con ceftriaxone
- Correzione idroelettrolitica ev

Trasferimento in reparto

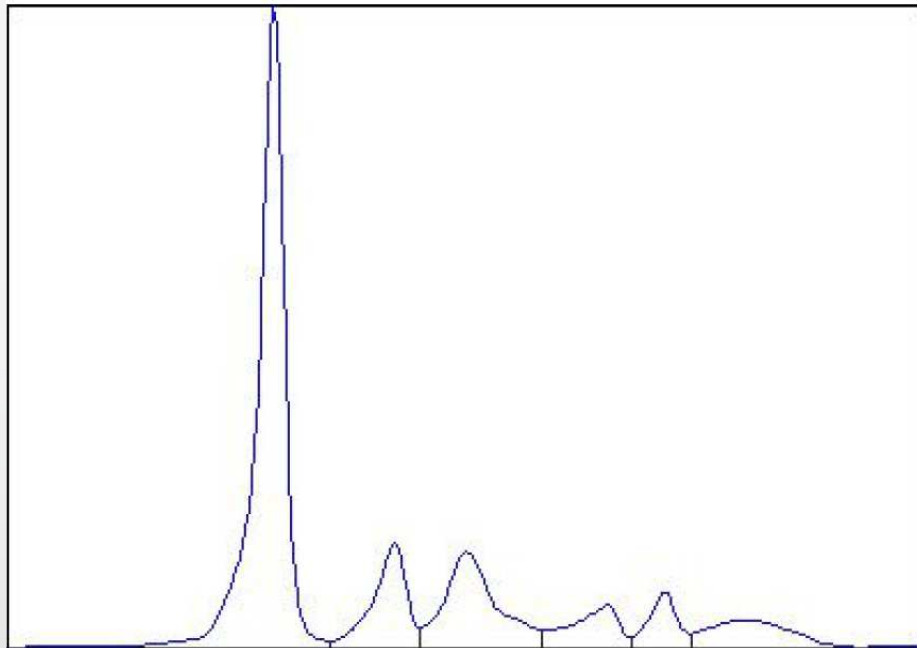
Immunoglobuline Ig G	<b>373</b>	L	mg/dl	610 - 1615
<i>Metodo Turbidimetrico</i>				
Immunoglobuline Ig A	<b>11</b>	L	mg/dl	84 - 500
<i>Metodo Turbidimetrico</i>				
Immunoglobuline IgM	<b>&lt;10</b>		mg/dl	35 - 245
<i>Metodo Turbidimetrico</i>				

**Ig Sottoclassi 1,2,3,4 (Ciascuna)**  
*Nefelometrica*

IgG 1	<b>209</b>	L	mg/dl	382 - 929
IgG 2	<b>119</b>	L	mg/dl	242 - 700
IgG 3	<b>19</b>	L	mg/dl	22 - 177
IgG 4	<b>3.7</b>	L	mg/dl	4.0 - 87.0

Rivalutazione status immunologico





#### Elettroforesi Proteica

Albumina	<b>55.50</b>	L %	55.80 - 66.00
Alfa 1	<b>10.80</b>	H %	2.90 - 4.90
Alfa 2	<b>15.50</b>	H %	7.00 - 11.80
Beta 1	<b>6.20</b>	%	4.70 - 7.20
Beta 2	<b>5.00</b>		3.20 - 6.50
Gamma	<b>7.00</b>	L %	11.00 - 18.80
Albumina #	<b>2.70</b>	L g/dl	3.90 - 4.70
Alfa 1 #	<b>0.50</b>	H g/dl	0.20 - 0.35
Alfa 2 #	<b>0.70</b>	g/dl	0.50 - 0.85
Beta 1 #	<b>0.30</b>	L g/dl	0.34 - 0.52
Beta 2 #	<b>0.20</b>	L g/dl	0.23 - 0.47
Gamma #	<b>0.30</b>	L g/dl	0.70 - 1.40
Rapporto A/G	<b>1.25</b>		1.10 - 2.40
Commento			

*Aumento delle proteine della fase acuta. Ipogammaglobulinemia*


## Rivalutazione status immunologico

El: Frammenti di mucosa del grosso intestino ad architettura sostanzialmente conservata. È presente aumento dell'infiltrato infiammatorio cronico e granulocitario neutrofilo della lamina propria che mantiene una normale distribuzione nell'ambito della lamina propria. Sono presenti numerose immagini di criptite ed erosioni superficiali. Si osserva focale distacco dell'epitelio superficiale.

**Il quadro istologico sopra descritto è complessivamente suggestivo di danno infettivo.**

## Esami diagnostici

- Esame parassitologico delle feci su singolo campione
  - negativo
- Coprocoltura Salmonella/Shigella/Campylobacter
  - Positiva per *Campylobacter Coli*
- Emocolture aerobi/anaerobi
  - negative



## Focus on: Campylobacter Coli

- Bacillo gram-negativo a virgola
- Responsabile del 5 % delle gastroenteriti da *Campylobacter* spp.
- È una zoonosi, nei paesi sviluppati l'infezione è causata principalmente da carne di maiale contaminata (ma anche da pollame, pecore e uccelli)
- Il quadro clinico più frequente è caratterizzato da diarrea, febbre e dolori addominali

PR Murray et al. Medical Microbiology. 8° edition. Elsevier. 2016

Valenza G, Frosch M, Abele-Horn M. Antimicrobial susceptibility of clinical *Campylobacter* isolates collected at a German university hospital during the period 2006-2008. Scand J Infect Dis. 2010;42(1):57-60.

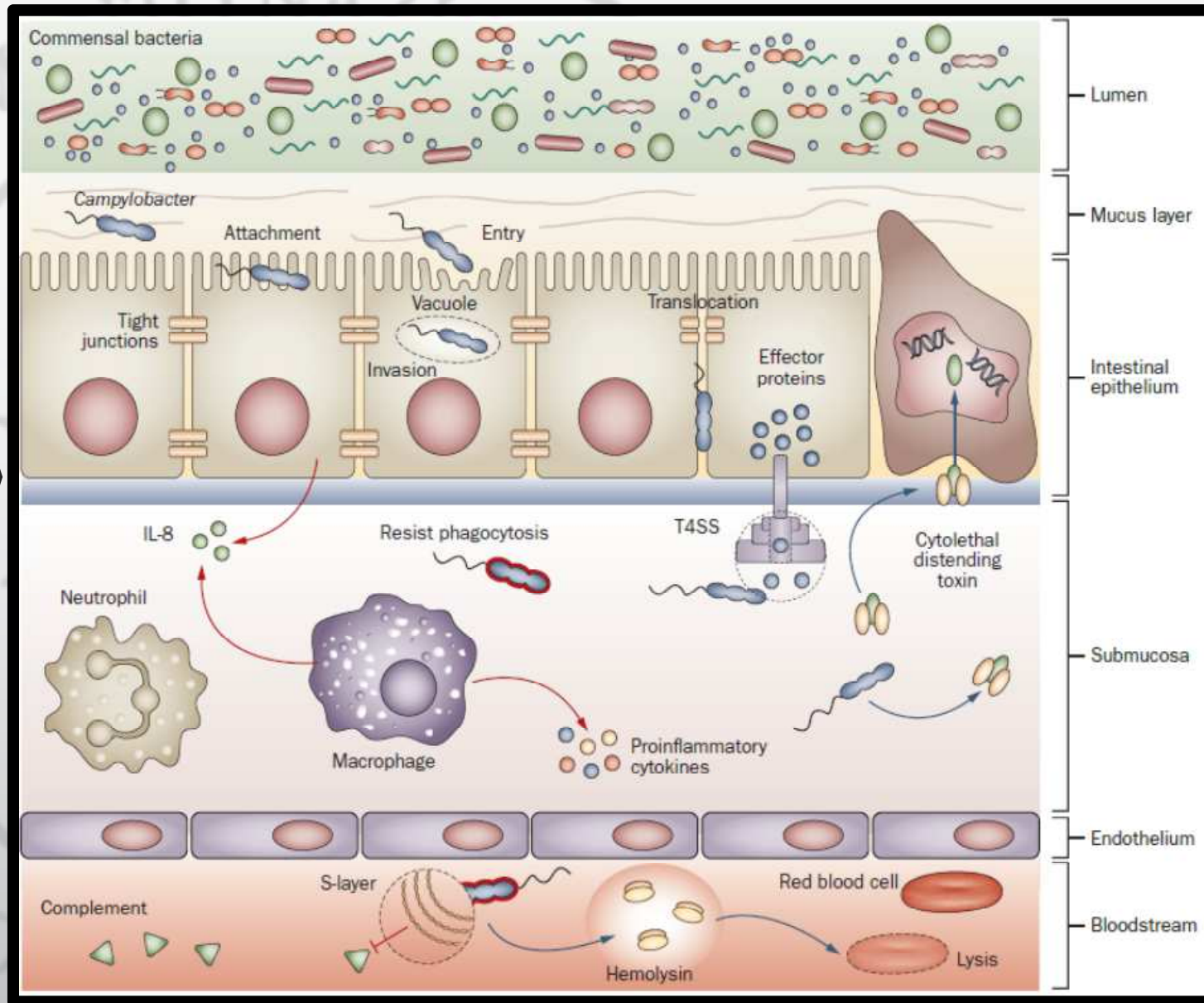
# Pathogenesis of gastroenteritis

- Cytolethal distending toxin (CDT) is the toxin produced by *Campylobacter* species including *C. jejuni*, *C. lari*, *C. coli*, *C. fetus*, and *C. upsaliensis* and induces cell distension in several mammalian cells via elongation and swelling, followed by cell death

- The mechanism of *Campylobacter* spp. gastroenteritis is as follows: the invading bacteria colonize the colon by passing through the mucosal layer of the gastrointestinal tract epithelium, and the bacteria reduce the intestinal absorption capacity by sticking to the surface of the colon cells



# Pathogenesis of gastroenteritis



Man SM. The clinical importance of emerging *Campylobacter* species. *Nat Rev Gastroenterol Hepatol*. 2011 Oct 25;8(12):669-85.

### Tossinfezioni alimentari

#### Informazioni generali

#### News

- ultimi aggiornamenti

#### Aspetti epidemiologici

#### Studi

#### Link

#### Strumenti dal territorio

Focolai di E. coli nei paesi Ue 2011

### tossinfezioni alimentari

## Report Ecdc Efsa 2017 su zoonosi e malattie a trasmissione alimentari: focus sulla situazione nazionale

Luca Busani<sup>1</sup>, Caterina Graziani<sup>1</sup>, Ida Luzzi<sup>1</sup>, Gaia Scavia<sup>1</sup>, Stefano Morabito<sup>1</sup>, Antonietta Gattuso<sup>1</sup>, Alfonsina Fiore<sup>1</sup>, Antonia Ricci<sup>2</sup>, Francesco Pomilio<sup>3</sup>

<sup>1</sup>Istituto Superiore di Sanità, Roma

<sup>2</sup> Istituto Zooprofilattico Sperimentale delle Venezie, Legnaro (PD)

<sup>3</sup> Istituto Zooprofilattico Sperimentale dell'Abruzzo e del Molise, Teramo

### Campylobacter

Come per gli anni precedenti, anche nel 2016 il numero di infezioni da *Campylobacter* si aggira intorno ai 1000 casi. Occorre sottolineare che la *campylobacteriosi* nel nostro Paese non è una malattia a notifica obbligatoria pertanto i dati disponibili derivano da attività di laboratorio che non hanno una copertura e una rappresentatività nazionale.

New:

25/1/2018 - Zoonosi trasmissione alimenti situazione nazionale

21/12/2017 - Zoonosi tossinfezioni alimenti Efsa il report 2017

Trova





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Surveillance and outbreak reports

# The first report on *Campylobacter coli* family outbreak detected in Poland in 2006

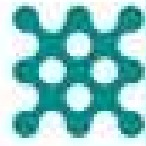
S Wardak<sup>1</sup>, J Szych<sup>1</sup>, M Sadkowska-Todys<sup>2</sup>

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[June 2006](#) Volume 12, Issue 6, Pages 561–570

[Next Article >](#)

## A large multi-pathogen waterborne community outbreak linked to faecal contamination of a groundwater system, France, 2000

[A. Galloway](#)  [H. De Valk](#), [M. Cournot](#), [B. Ladeuil](#), [C. Hemery](#), [C. Castor](#), [F. Bon](#), [F. Mégraud](#), [P. Le Cann](#), [J.C.](#)

# Terapia

- Antibiotics may be indicated if any of the following occur:
  - High fever
  - Bloody diarrhea
  - Excessive bowel movements (ie, >8 stools per day)
  - Worsening symptoms
  - Failure of symptoms to improve
  - Persistence of symptoms for longer than 1 week
  - Pregnancy
  - HIV infection and other immunocompromised states

Drugs & Diseases > Infectious Diseases

## Campylobacter Infections

Updated: Jun 16, 2017 | Author: Mahmud H Javid, MBBS; Chief Editor: Michael Stuart Bronze, MD more...

# Terapia

- ***Azithromycin*** therapy would be a primary antibiotic choice for *Campylobacter* infections, when indicated with a typical regimen of 500 mg/d for 3 days. However, erythromycin is the classic antibiotic of choice.
- The use of fluoroquinolones in food animals has resulted in fluoroquinolone-resistant *Campylobacter* strains worldwide.

Bolinger H, Kathariou S. The Current State of Macrolide Resistance in *Campylobacter* spp.: Trends and Impacts of Resistance Mechanisms. Schaffner DW, ed. *Applied and Environmental Microbiology*. 2017;83(12):e00416-17.

# Dimissione

- Esami ematochimici

GR (4,4-10,6 10 <sup>6</sup> /uL)	Hb (13,0-18,0 g/dl)	Hct (42-52%)	MCV (85-98 fl)	GB (4,3-10,8 10 <sup>3</sup> /uL)	L (16-45%)	PCR (0-0,5 mg/dl)	K+ (3,5- 5,5 mmol/l)
2,8	10,5	30	<b>107</b>	4980	63,1	<b>0,5</b>	<b>4,3</b>

- Riduzione del numero delle evacuazioni ed aumento consistenza delle feci

1 mese dopo

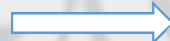
1. Follow-up:

- Esame parassitologico delle feci su singolo campione
  - negativo
- Coprocoltura Salmonella/Shigella/Campylobacter
- negativo Miglioramento condizioni cliniche generali
- Incremento ponderale
- Cessazione della sintomatologia



# Test microbiologici effettuati

- Parassitologico su singolo campione
  - Oocisti di *Cryptosporidium* spp.
- Coprocoltura
  - Positiva per *C. coli*



Tp con Metronidazolo, mancata risposta clinica



Tp con Azitromicina, apparente risoluzione della sintomatologia

Stark D, Barratt JL, van Hal S, Marriott D, Harkness J, Ellis JT. Clinical significance of enteric protozoa in the immunosuppressed human population. Clin Microbiol Rev. 2009 Oct;22(4):634-50

- Laboratory diagnosis of cryptosporidiosis traditionally relies on special staining techniques, such as modified acid-fast, Kinyoun's, and Giemsa stains, as oocysts are difficult to detect using basic light microscopy.
- Oocysts are small (4-6  $\mu\text{m}$  in diameter) and can be missed without a very careful examination of the slide.
- Because shedding may be intermittent, examine at least 3 stool specimens collected on separate days before considering the test results negative.
- Other alternative diagnostic techniques have also been employed (Direct fluorescent immunoassay, EIA, or NAAT).

---

# Identificazione Cryptosporidium spp



- After an incubation period of 5-10 days (range 2-28 days), an infected individual develops watery diarrhea, which may be associated with abdominal cramps. [...] Fever may occur in 30-60% of patients.
- Diarrhea, with or without crampy abdominal pain, may be intermittent and scant or continuous, watery, and copious; sometimes, the diarrhea is mucoid. It rarely contains blood or leukocytes. **Relapses may follow a diarrhea-free period of several days to weeks.** Diarrhea can persist longer in immunocompromised people, particularly those with impaired cell-mediated immunity
- The drugs paromomycin, azithromycin, and nitazoxanide have been shown to reduce the parasite load

## Diarrea da *Cryptosporidium* spp

Shane AL et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. Clin Infect Dis. 2017 Nov 29;65(12):1963-1973.

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