Management of *Clostridium difficile* infection

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Case I

- 79-year old patient admitted to hospital due to infective exacerbation of chronic obstructive pulmonary disease (COPD)
- Treated with levofloxacin for 2 weeks
- Discharged home in good condition
- Next 5 days: did well
- On days 6: did not feel well, attended practitioner
- Another 10 days later: presented at hospital with Fever, no appetit, dehydrated, dyspnea, diarrhoea, chest pain left, and left upper quadrant abdominal pain

Case I – Physical examination

79-year old woman, reduced general condition, oriented
no edema, tongue dry, no cyanosis,
Heart rate: 84 beats/min.
respiratory rate: 15/min.
blood pressure: 140/70 mmHg
temperature: 38°C

Heart: regular rate and rhythm,
systolic murmur left sided upper sternal edge

Chest: vesicular breathing, isolated wheezes

Abdomen: soft and nontender

Case I – Laboratory findings

In normal range:

urea, creatinine, transaminases (ALT, AST, gamma –GT), alkaline phosphatase, LDH, blood count, urine profile (except ketone bodies), thyroid function, lipids

Not in normal range:

uric acid 7.7(↑), calcium 2.05 (↓), CRP 14 mg/dl (↑), segmented neutrophils 67% (↑), monocytes 13% (↑), lymphocytes 16.5 % (↓), ketone bodies in urine 5 (↑), potassium 3.1 mmol/l (↓), sodium 146 mmol/l (↑)

Case I – Medical history

- **Previous medical history**:
  - hypertension, aortic sclerosis
  - polyneuropathy legs
  - chronic obstructive pulmonary disease (COPD)

- **Acute problem/presentation**:
  - Pain and feeling of pressure in the left lower chest and upper bowel quadrant
  - Bowel movements: watery, non-bloody diarrhea (10 x/day), greenish
  - no consumption of not-well cooked meat/poultry in the last 2 weeks drank less than 1l/day
    no travel history in the last year (Italy 7 years ago)

Case I - Premedication

Pantoloc (pantoprazole, PPI) 40,
Capozide/HCT (Captopril, ACE- inhibitor and hydrochlorothiazide, diuretica)1/2,
Respicur (bronchodilatator) 200,
Spiriva (tiotropium bromide, COPD treatment),
Oxis (formoterol fumarate dihydrate, ß2-adrenergic stimulant) 2x1,
Berodual (Ipratropium bromide)
Thrombo ASS,
Maxi Calc D3,
Neurontin (anti-epileptic, treatment of nerve pain) 300 1-0-1,
Temesta (benzodiazepine) 1mg 0-0-0-1,
Dominal forte (prothipendyl),
Neurobion forte (Vit. B complex)

Case I

- **ECG**: SR normal, no ST elevation or depression, small T wave

- **abdominal X-ray:**
  No hint for free abdominal air
  No hint for ileus
  Marked coprostasis and meteorism in large bowel

Case I

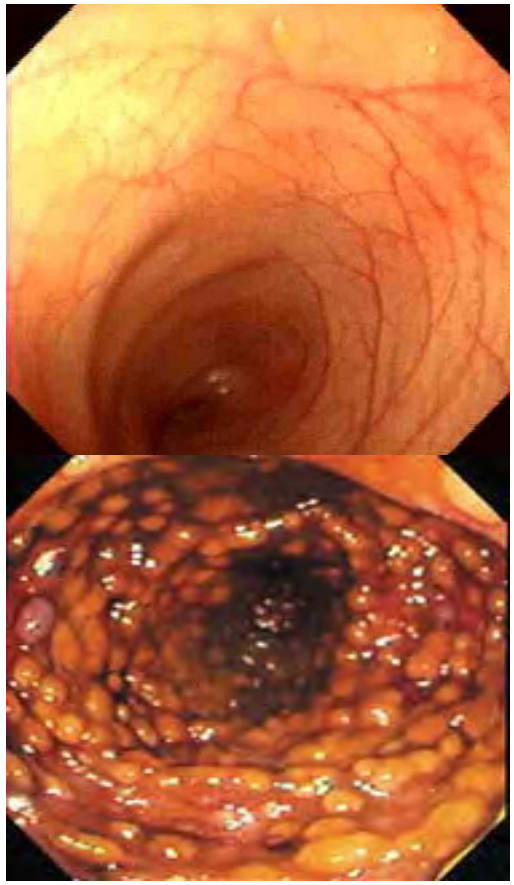
- What are the differential diagnoses?

Case I

- What are the symptoms of *Clostridium difficile* infection?

Symptoms of *Clostridium difficile* infection (CDI)

- Asymptomatic colonization
- Diarrhea
  - mild → moderate → severe
- Abdominal pain and distension
- Fever
- Pseudomembranous colitis
- Toxic megacolon
- Perforated colon → sepsis → death



Markers of Severe Disease

- Leukocytosis (>15 x 10^9/l)
- Albumin low (<30g/l)
- Creatinine (>133µm or >1.5 times the premorbid level)
- >10 BM/day
- Pseudomembranous colitis
- Toxic megacolon
- Severe distension and abdominal pain

Case I

- What are her risk factors to acquire *Clostridium difficile* infection?

Risk factors for Infections with *C. difficile*

- Broad spectrum antibiotics,
  esp. Fluorquinolons, Clindamycin, Amoxicillin, Cephalosporins,
  Penicillin-inhibitor compounds (e.g. ampcillin+ clavulanic acid)

  Risk of CDI is elevated (7-10 fold) during and in the 3 months following antimicrobial therapy
  85-90% of CDI occur within 30 days of antimicrobial exposure
  one single dose enough to cause CDI

- Age (>65 years) (CDI risk 10 fold higher)

- Longer hospital stay (<3 days)

Chang et al., Infect Control Hosp Epidemiol 2007
Hensgens et al., J Antimicrob Chemother 2012

Risk factors for Infections with *C. difficile*

- Chemotherapy
- proton pump-inhibitor
  H2 receptor antagonists increase risk by 53%
  daily proton pump inhibitor therapy increases the risk by 74%
- Intraabdominal surgical intervention
- Severe comorbidity

Case I

- How did she acquire *Clostridium difficile*? What is the pathogenesis?

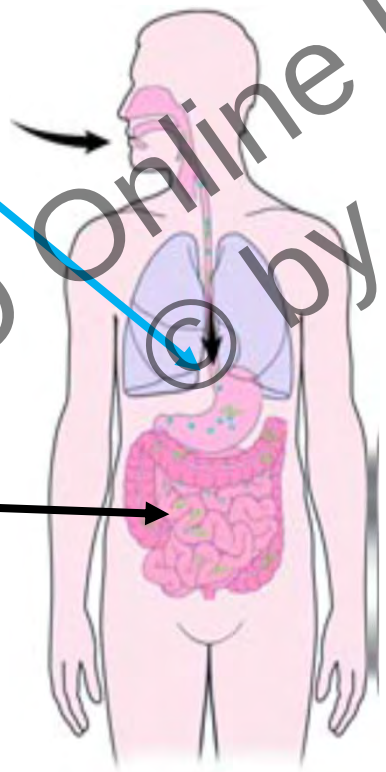
Pathogenesis of CDI

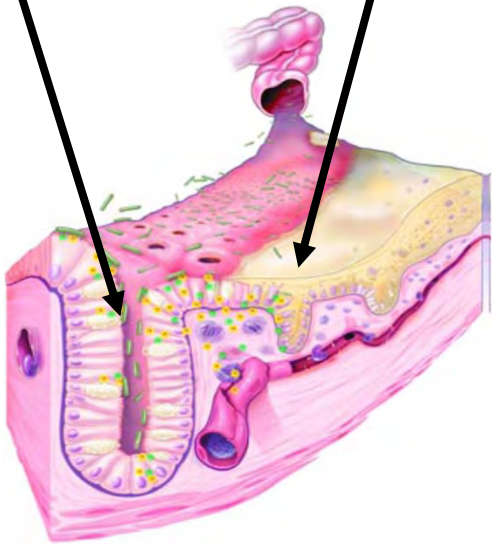
1. CDI spores survive in the environment for long periods of time. Following ingestion, they traverse the acidic environment of the stomach.

2. Spores germinate within the intestine.

3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon.

4. Toxin A & B Production leads to colon damage +/- pseudomembrane.





Sunenshine & McDonald, Clin J Med 2006.

Toxins

- Toxigenic *C. difficile* isolates produce:
  - Toxin A and/or
  - Toxin B

    regulation by positive (TcdR) and negative (TcdC) regulators
  - binary toxin (role still unknown)

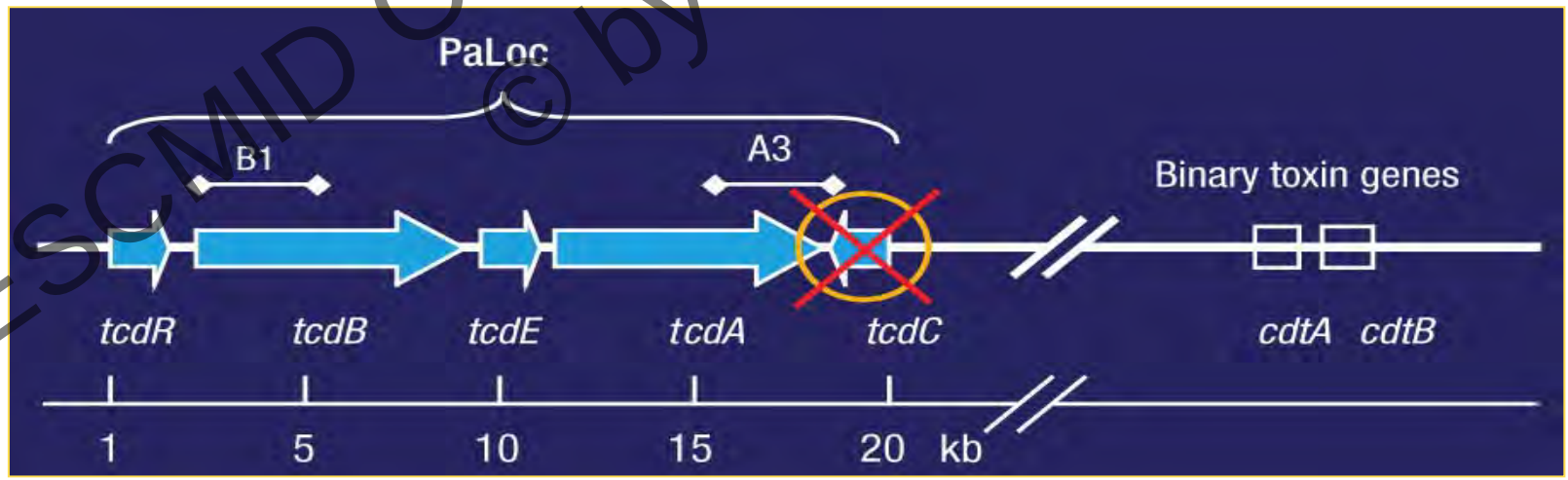
    By itself, not pathogenic

    May act synergistically with toxins A and B in severe colitis

    More common in animal strains

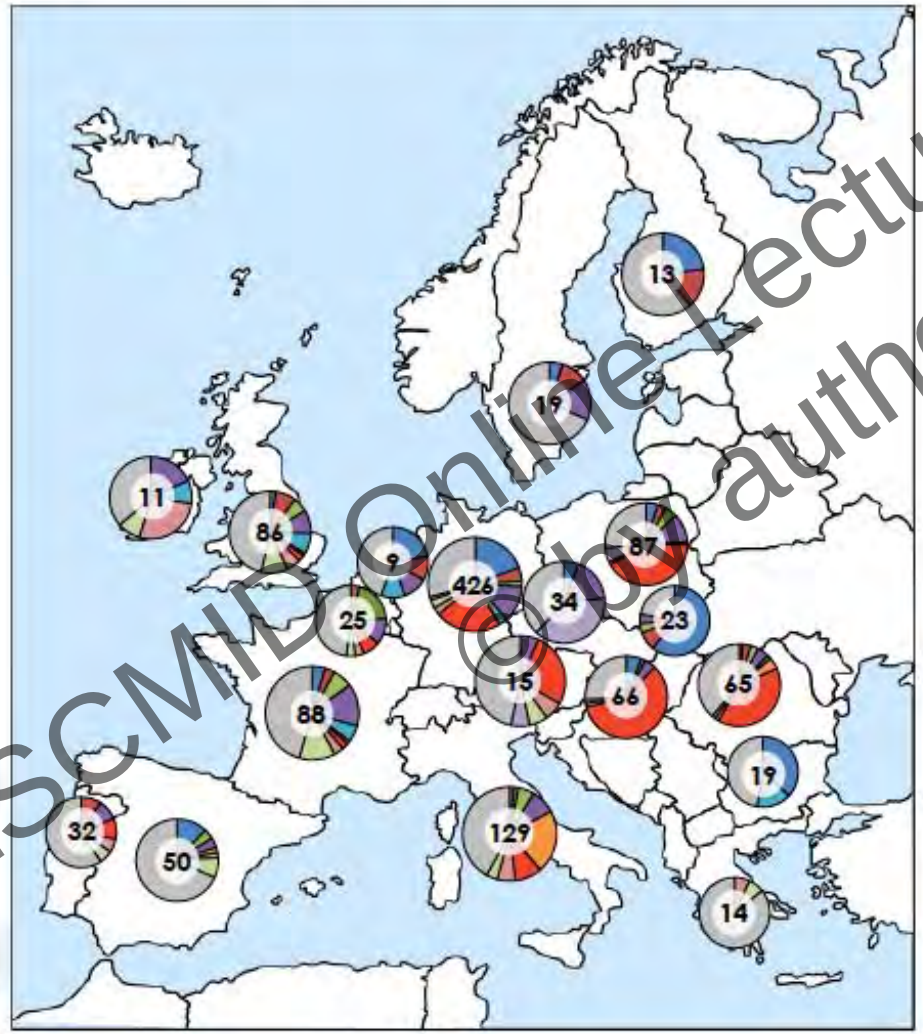
Epidemic Strain RT027

- highly resistant to fluoroquinolones
- Binary toxin genes are present
- Produces large quantities of toxins A and B (*tcdC* gene deletion)
- reduced response to Vancomycin and Metronidazol
- association with higher rate of recurrence and lethality (up to 30%)



Adapted from McDonald et al., N Engl J Med 2005
Warny M et al., Lancet 2005
Hubert B et al., Clin Infect Dis 2007

Distribution of *C. difficile* ribotypes in Europe – Data from EUCLID (2013)



Ribotype (proportion)

- 001/072 (11.1%)
- 002 (4.0%)
- 010 (3.4%)
- 014/020 (10.2%)
- 015 (2.5%)
- 018 (3.0%)
- 027 (18.4%)
- 078 (3.1%)
- 140 (4.0%)
- 176 (2.1%)
- Other (n=109)

Davies KA, et al. Lancet ID. 2014.

Case II

- 75 year old patient,
- past medical history:
  apoplexy one year ago
  hypercholesterinaemie
  Hypertension
  recurrent infections thus often for treatment at his family doctor
- Acute problem:
  Since 5 weeks diarrhoea, stool: in the beginning dark brown, malodoront, now getting brighter and liquid, incontinence
  weight loss (6 kg), dietary food since 2 weeks
  marked weakness,
  No pulmonary or cardiac complaints, no fever, no allergy, no pets, no consumption of raw milk

Case II

- Medication:
  Lansobene (Lansoprazole, PPI) 30mg,
  Simvastatin,
  Amlodipin (calcium channel blocker),
  Alna ret (alpha blocker),
  Zoldem (treatment of insomnia),
  Neurofenac (Diclofenac),
  Dancor (vasodilatory drug),
  Immodium (Loperamide),
  Antibiophilus (Lactobacillus probiotic)

- Physical examination:
  reduced condition, auscultation without pathological findings, abdomen diffusely tender to palpation

Case II - Laboratory findings

Glucose	82 mg/dl	(70 – 110)
Urea	32.3 mg/dl	(10.0 - 50.0)
Creatinine	**1.52 mg/dl**	**(0.70 - 1.20) ->**
Glomerular filtration rate	47.7 ml/min/1,73m²	
Uric acid	6.91 mg/dl	(2.40 - 7.50)
Sodim	142 mmol/l	(135 – 145)
Potassium	3.6 mmol/l	(3.4 - 4.6)
Chloride	109 mmol/l	(98 – 108) ->
AST	27 U/l	(10 – 50)
ALT	22 U/l	(10 – 50)
Gamma-GT	12 U/l	(10 – 60)
Alkaline Phosphatase	60 U/l	(40 – 130)
Lactat-Dehydrogenase (LDH)	192 U/l	(100 – 250)
C-reactive prot. (CRP)	**5.30 mg/dl**	**(0.00 - 0.70)->**

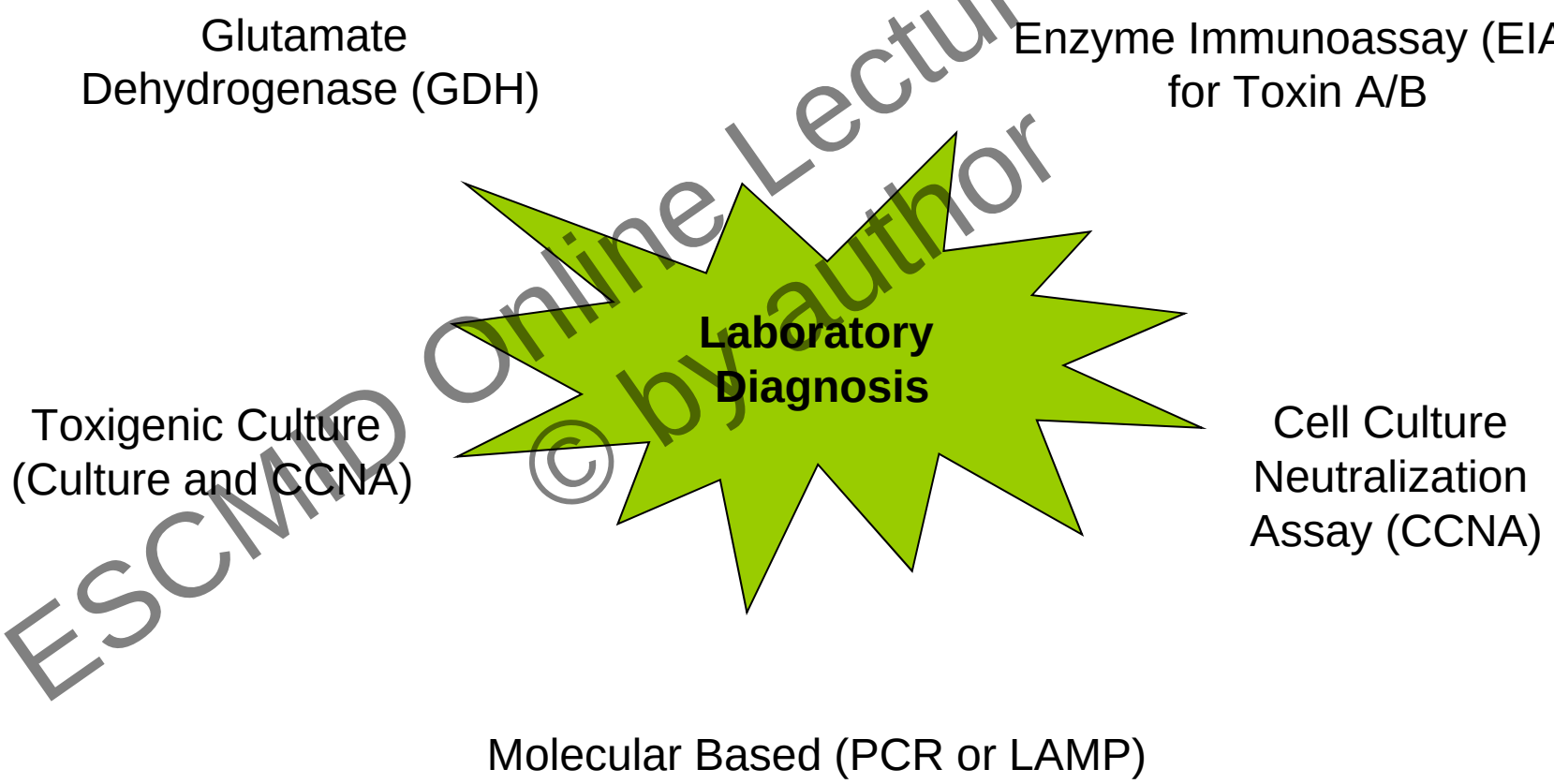
Case II - Laboratory findings

Leukocytes	**26.2 G/l**	**(4.0 - 10.0)** ->
Absolute Neutrophile count	4.2 G/l	(2.0 - 7.0)+
Red blood cells	3.67 T/l	(4.40 - 5.90) <-
Hemoglobin	**112 g/l**	**(130 – 177) <-**
Hematocrit	0.327 l/l	(0.400 - 0.520) <-
Platelet count	282 G/l	(150 – 380)
MCH	30.5 pg	(27.0 - 32.0)
MCV	89.1 fl	(77.0 - 96.0)
Red cell distribution width	13.2 %	(11.0 - 16.0)
Differential:		
Segmented Neutrophils	67.0 %	(46.0 - 66.0) ->
Lymphocytes	18.0 %	(20.0 - 40.0) <-
Lymphocytes absolut	1.12 G/l	(0.80 - 4.00)
Monocytes	11.9 %	(2.0 - 10.0) ->
Eosinophils	2.9 %	(1.0 - 5.0)
Basophils	0.2 %	(0.0 - 1.0)

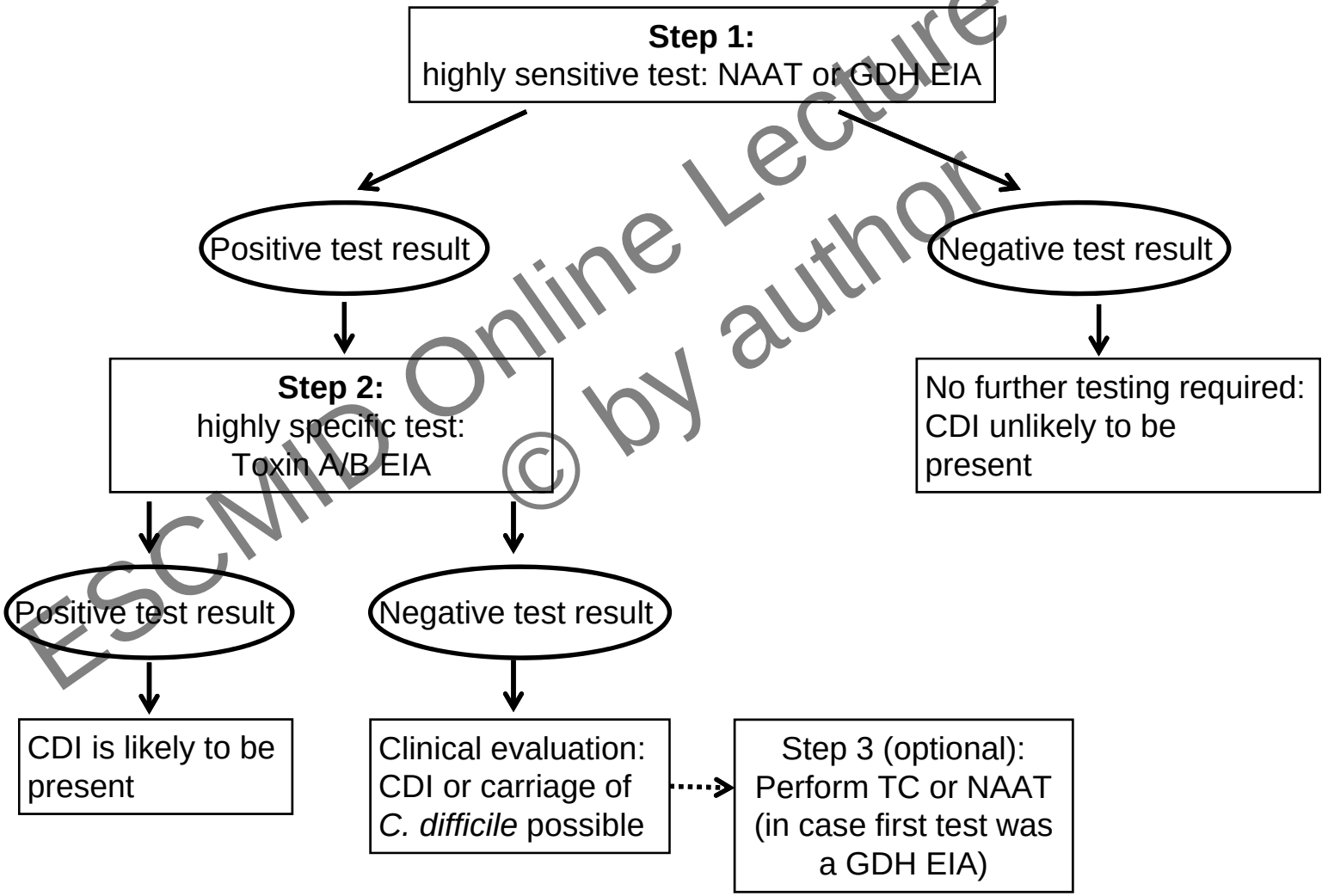
Case II

- Which microbiological tests would you perform?

Laboratory Diagnosis of CDI

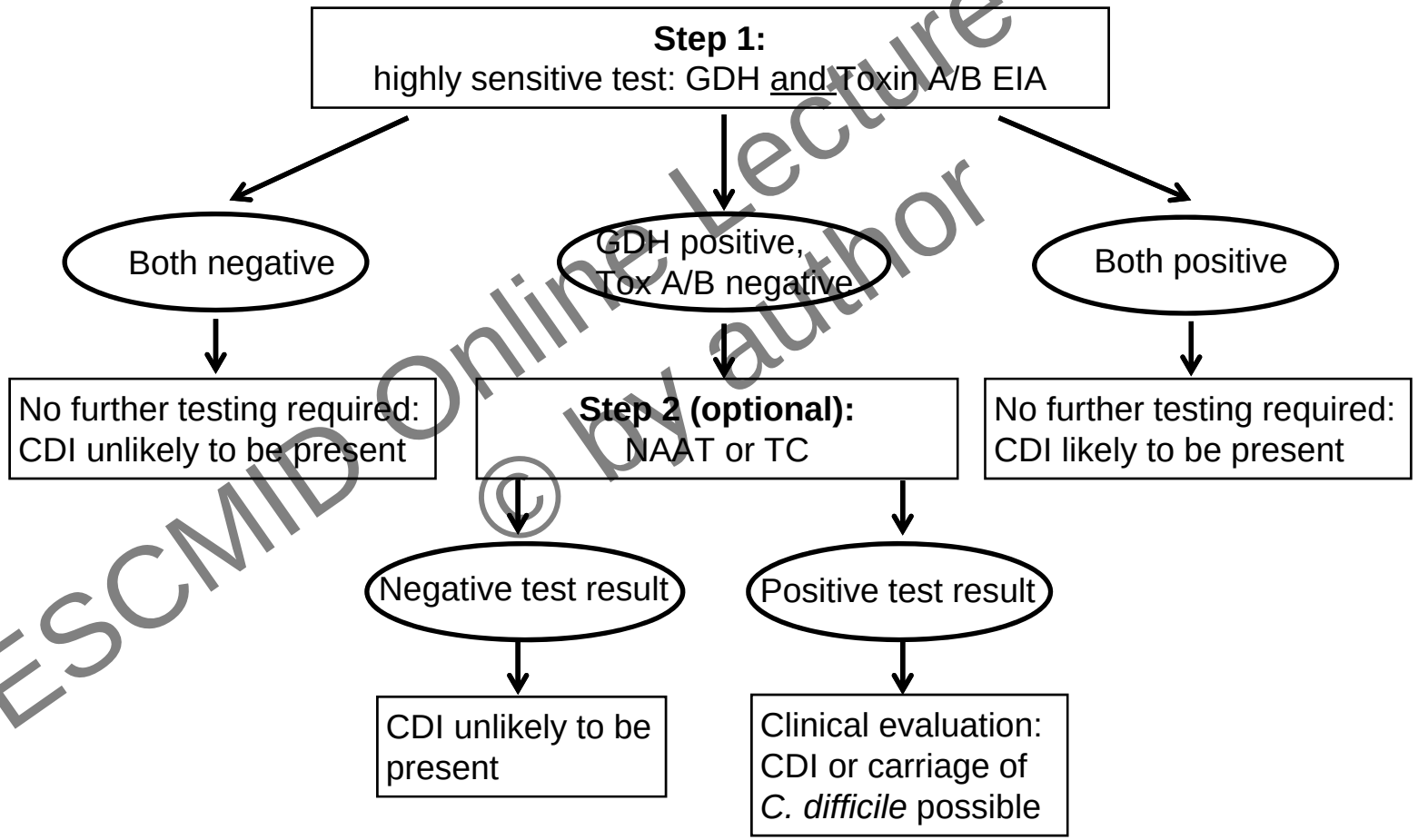


Laboratory testing



Crobach et al., Clin Microbiol Infect 2016

Laboratory testing



Crobach et al., Clin Microbiol Infect 2016

Case II

- Which specimen would you take for microbiology? And what do you have to consider concerning the specimen?

Specimen: Stool

- Fresh is best (test within 2 hours)
- Liquid or loose, not solid (exception: ileus)
- If unable to test within 2 hours, refrigerate at 4˚ C for up to 3 days
- Freeze at -70˚ C (not -20˚ C) if testing will be delayed
- Specimen quality will influence test results
- Do not test specimen for confirmation of therapy success

Therapy – CDI

- discontinue current antibiotic therapy if clinically possible
- Fluid therapy
- Metronidazole
- Vancomycin
- Fidaxomicin (macrocyclic antibiotic)
- Fecal transplantation
- Surgery (colectomy)
- Alternative treatment options:
  intravenous immunoglobuline G (bind to/ neutralize toxins),
  Probiotics?.....

Therapy – CDI

Mild to moderate disease:

- Metronidazole: 3 x 500 mg (4 x 250 mg) oral
  (if oral treatment not possible i.v.), 10-14 days
- Vancomycin: 4 x 125 (-250 mg) oral or nasogastric tube
  10-14 days

Severe disease:

- Vancomycin: 4 x 125 (-250 mg) oral, 10-14 days
  or intracolonic instillation by enema
  (0.5 – 1g Vancomycin i.v. formulation in 0.1 – 0.5 l of normal saline via rectal catheter, clamp for 60 min., repeat every 4-12 hours)
  Can add metronidazole (i.v.)
- Fidaxomicin 2 x 200 mg, 10 days
- Surgery?

Therapy – recurrent CDI

1st recurrence:

- Therapy as first episode (according to disease severity)

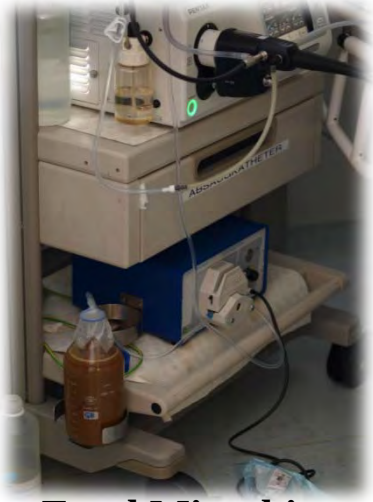
multiple recurrence:

- Vancomycin taper therapy:

  1st week: 4 x 125 mg
  2nd week: 2 x 125 mg
  3rd week: 1 x 125 mg
  4th week: 125 mg every 2nd day
  5th-6th week: 125 mg every 3rd day

- Fidaxomicin 2 x 200 mg, 10 days
- Fecal transplantation (combined with oral antibiotic)
  Rationale: restoration of bacterial homeostasis
  High cure rate (89% after a single FMT) and low relapse rate

Fecal Microbiota Transplant (FMT)



Donor

- Exclusion of infections (HIV, Hepatitis, Syphilis, CMV, EBV, blood count, renal and liver parameters; in stool: C. diff, GI-bacteria, viruses, parasites)
- No antibiotics for 3 months
- No GI problems (IBD)

Material preparation

- max. 6 hours
- Dilute in NaCl and mix
- Filtrate 2-3x
- in 50ml syringe

Fecal Microbiota Transplant

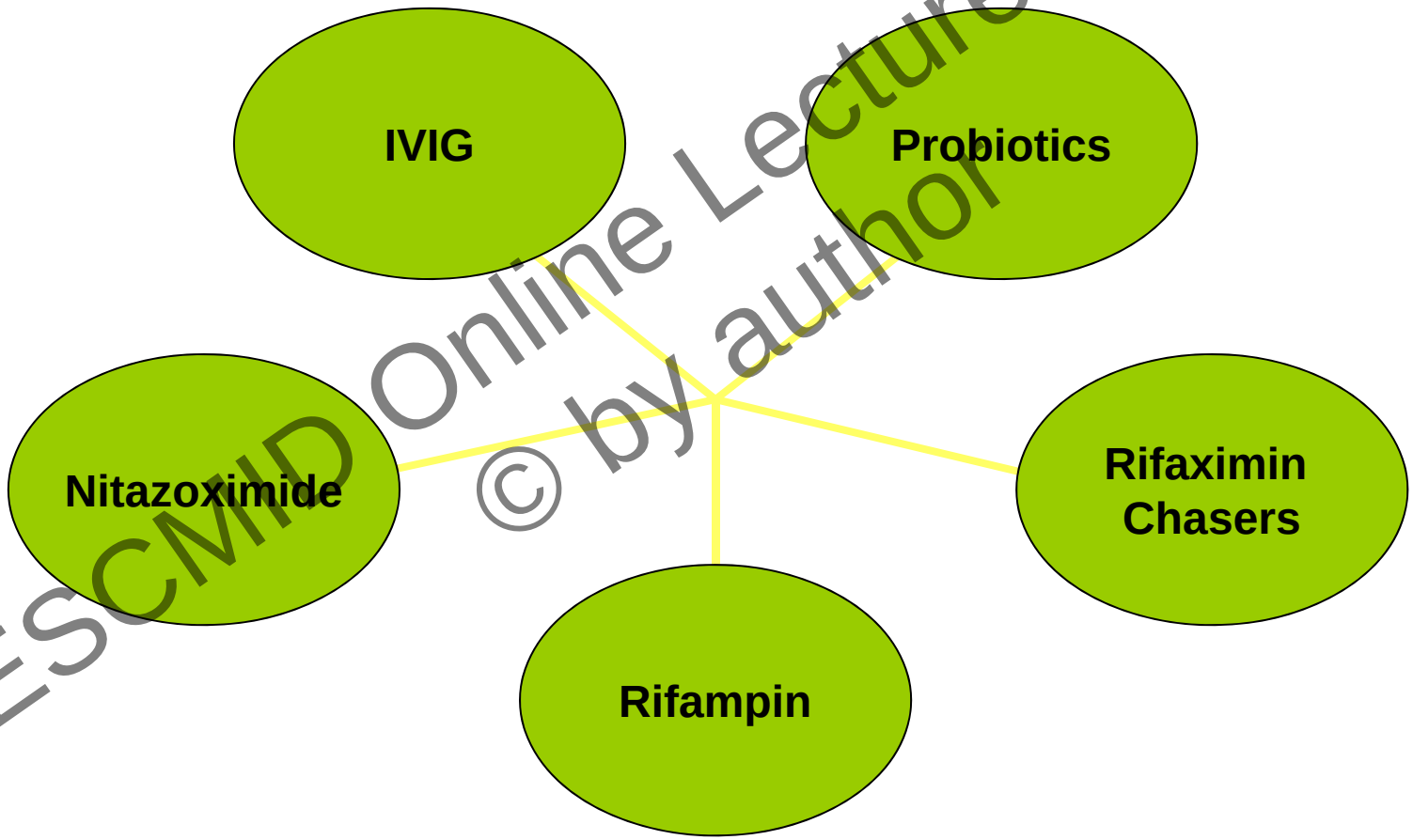
Via enema, nasogastric tube or colonoscopy

C. difficile Infection: Case III

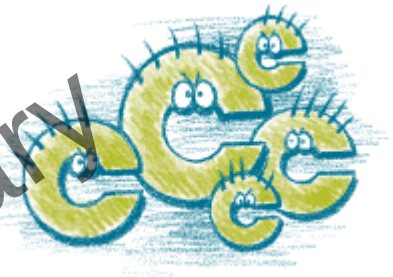
- 79-year-old woman with multiple medical problems admitted to hospital for treatment of community-acquired pneumonia
- Responds slowly to levofloxacin 750 mg daily
- After 6 days: develops diarrhea (9 loose BMs), WBC count: 11,500/mm^3
- Day 7: 14 loose BMs, WBC count rises to 19,500/mm^3
- Stool testing for *C. difficile* toxins A and B is requested
- Continued antibiotic therapy for pneumonia is deemed necessary

- How would you manage her care?
  A. Await stool test results and monitor her progress
  B. Empirically start metronidazole PO
  C. Empirically start metronidazole IV
  D. Empirically start vancomycin PO

Other Treatments



C. difficile Infection: Case III



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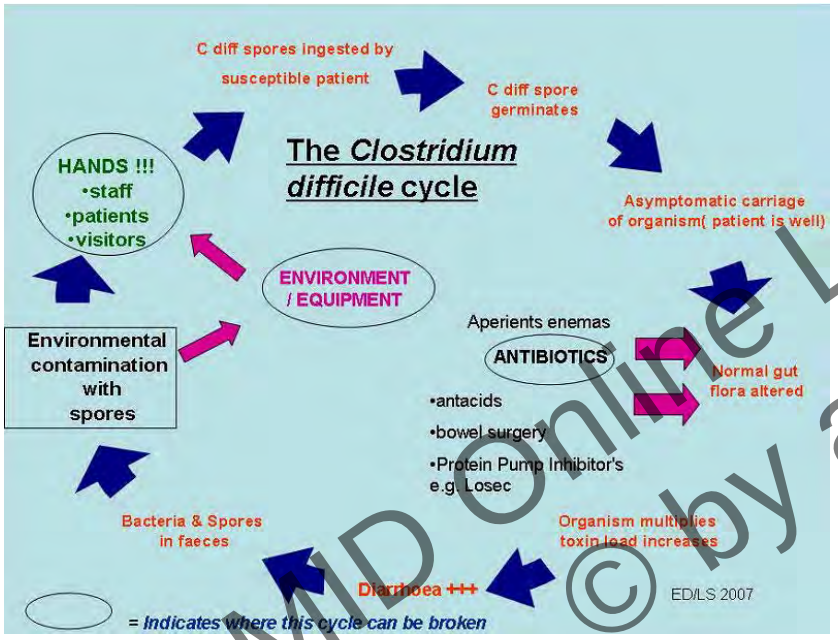
- Responds slowly to levofloxacin 750 mg daily
- After 6 days: develops diarrhea (9 loose BMs), WBC count: 11,500/mm^3
- Day 7: 14 loose BMs, WBC count rises to 19,500/mm^3
- Stool testing for GDH and *C. difficile* toxins positive
- Continued antibiotic therapy for pneumonia is deemed necessary

- Which hygienic precautions should be taken?
  - A. No precautions, hand disinfection sufficient
  - B. Barrier precautions
  - C. Single room with own toilet
  - D. Single room with own toilet and gloves, grown, mask upon patient contact

Infection control – important information



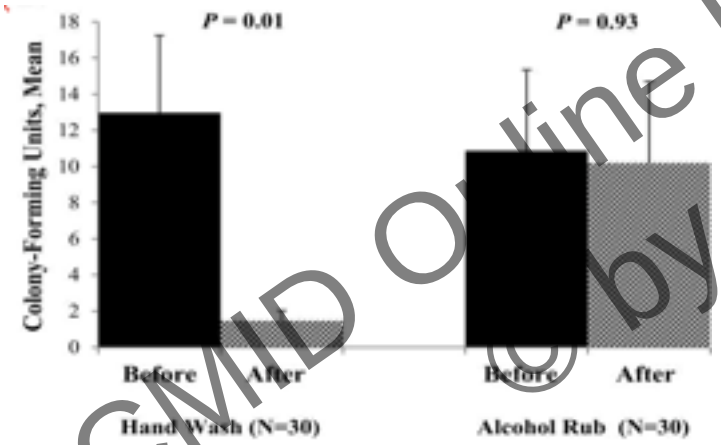
- Spores extremly resistant in environment
(against temp. >100°C, drying and also against antibiotics and disinfectants)
(Spores are not a reproductive form, they represent a survival strategy)

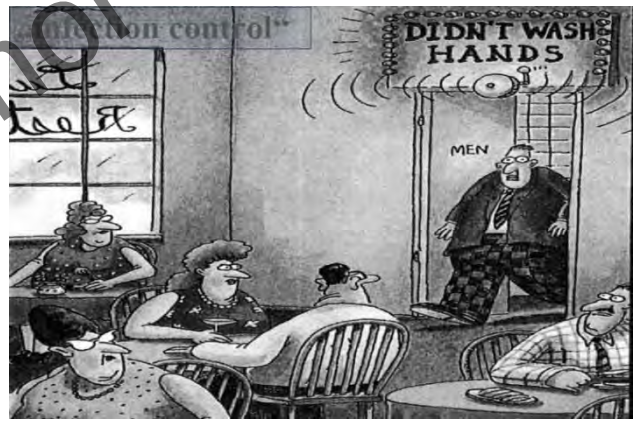
- other potential sources:
  - asymptomatic/colonized patients
    (3% in community, 20-40% in hospital patients)
  - environmental sources (water, farm animals or pets, food)

- Low infectious dose and massive fecal elimination by diarrhoeal patients (10^7 to 10^9 bacteria per gramm stool)

CDI – Infection control

- Strict hand hygiene
  (due to environmental resistance of the spores
  intensive hand washing + hand disinfection + gloves)





- accomodation of patients:
  - Isolation of patients with massive diarrhoea in single rooms with own toilette
  - in case of mild symptoms contact isolation with own toilette

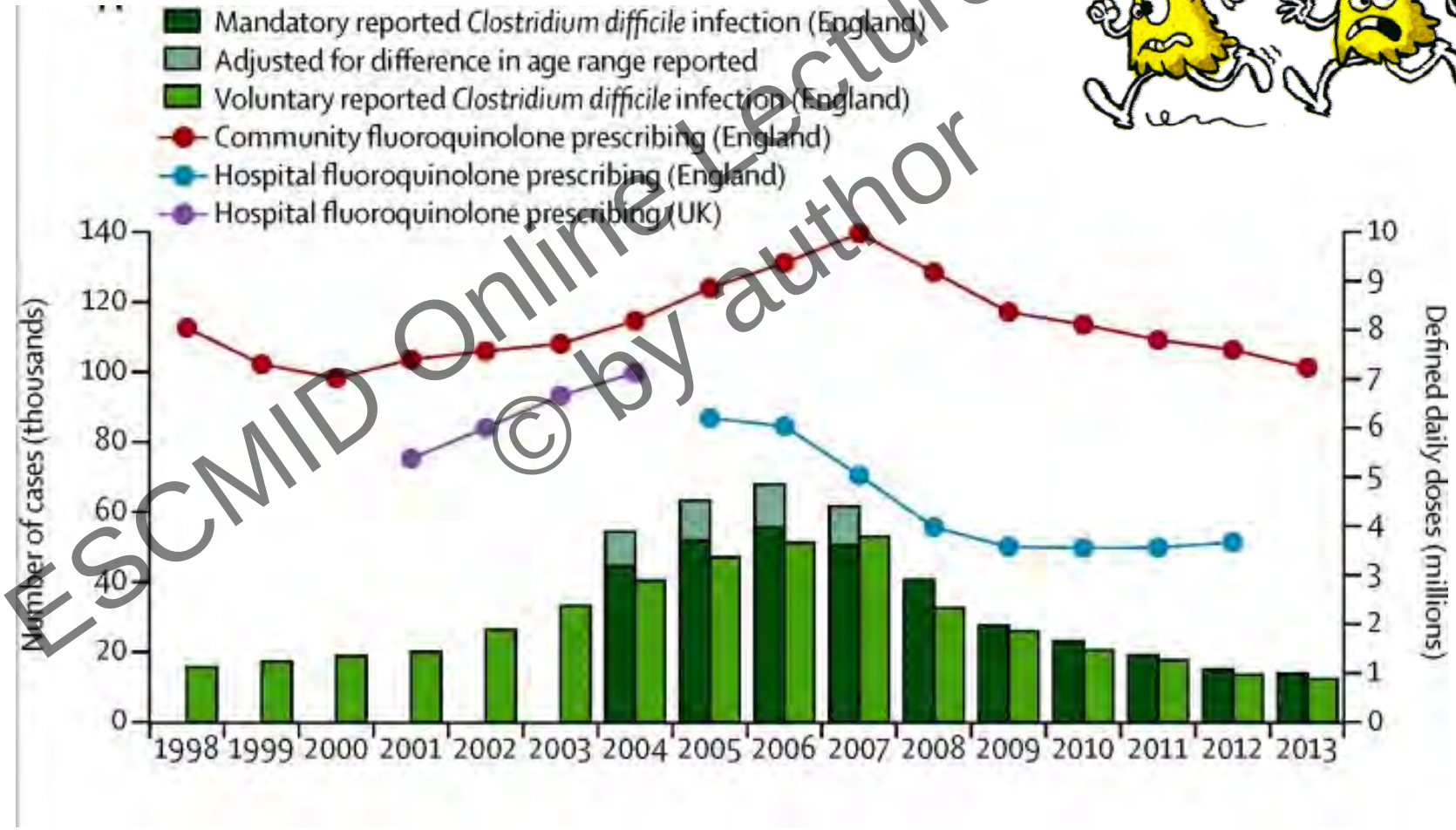
Kundrapu et al., Infect Control Hosp Epidemiol 2014

CDI – Infection control

- gowns required for direct contact
- Removal/thorough cleaning of environmental sources can decrease incidence
  Use sporicidal disinfectants
- Rationale antibiotic therapy for prevention

Kundrapu et al., Infect Control Hosp Epidemiol 2014

Effect of antimicrobial stewardship



Dingle et al., Lancet Infect Dis 2017

Transmission of *C. difficile*

- Investigation of 957 *C. difficile* isolates from CDI patients by whole genome sequencing
- 333/957 (35%) genetically related, 65% genetically distinct
  - 126/333(38%) ward contact with previous genetically related case
  - 55 cases had any hospital contact
  - 15 cases had same practitioner
  - 17 lived in same area
  - 120 no known contact
- The majority of *C. difficile* cases is not transmitted from another symptomatic patient
- Should we change our infection control strategies?

Eyre et al., N Engl J Med 2013