County Durham and Darlington NHS
NHS Foundation Trust

Clostridium difficile in Primary Care

Deepa Nayar, Consultant Microbiologist, CDDFT

NECS Antimicrobial Stewardship Workshops

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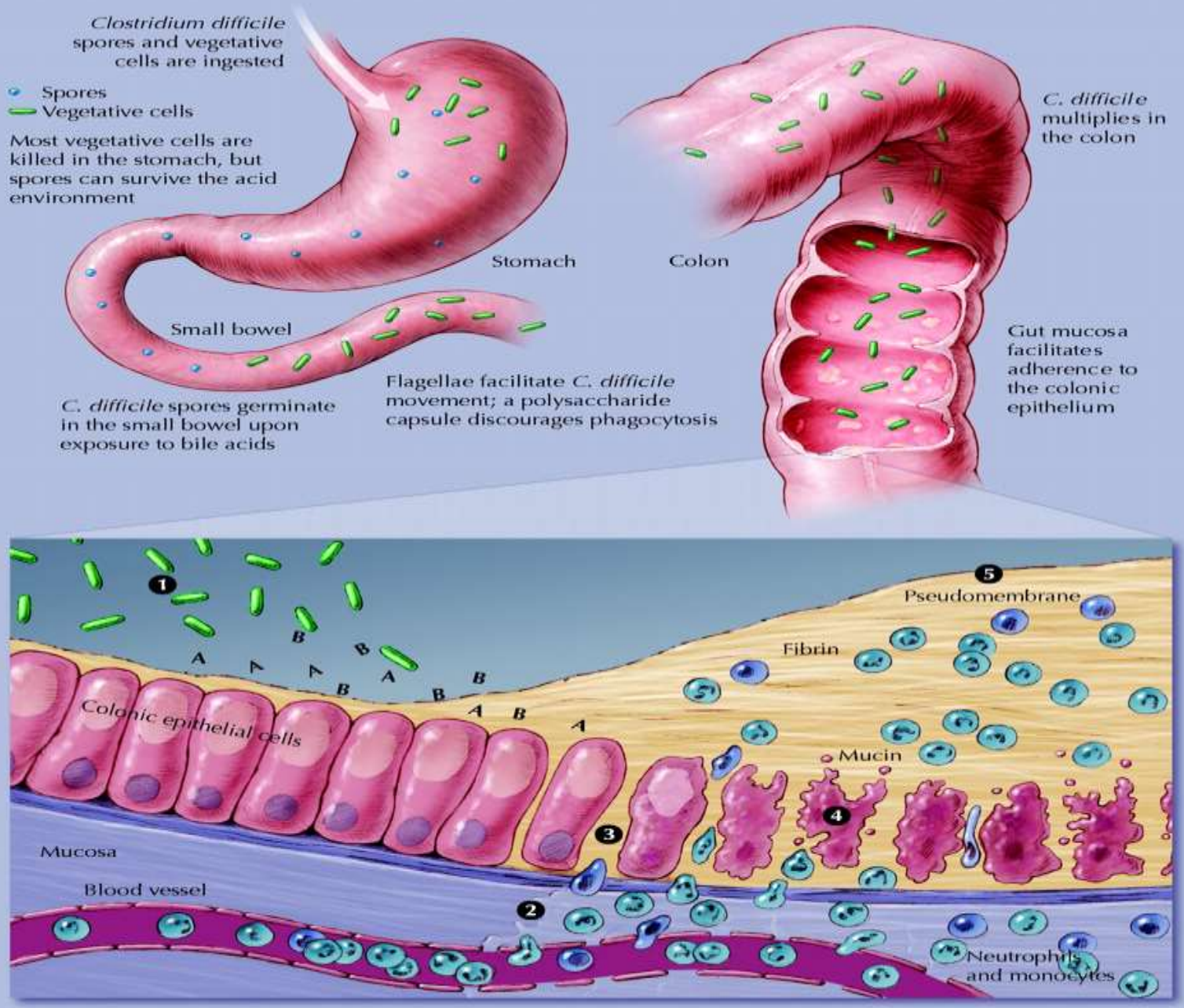
with you all the way

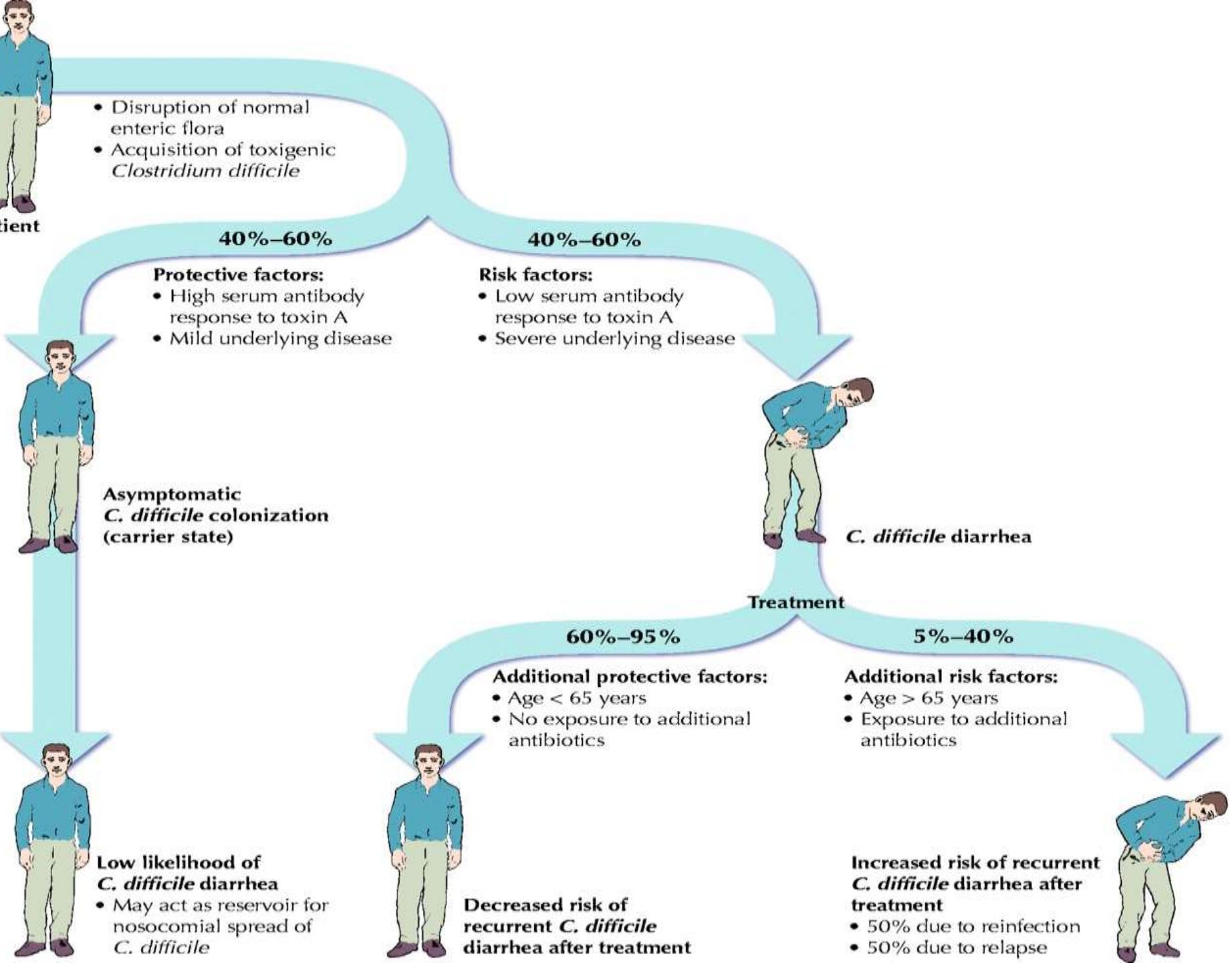
Clostridium difficile

- Gram positive rod
- Anaerobic
- Spore forming
- 60% neonates
- 2-3% of general population
- 10-20% of patients in hospital for 1-2 weeks rising up to 30% in those in hospital for 3-4 weeks

- *Clostridium difficile* infection (CDI), an infection of the large intestine, is the leading cause of healthcare-associated diarrhoea in Europe.
- CDI is usually a consequence of antibiotic use and most cases occur in the elderly.
- In severe cases CDI can cause serious bowel conditions that can be life threatening.
- CDI is common in hospitals and is increasingly recognised by experts as a problem in the community.
- In addition to its impact on individual patients, CDI accounts for a substantial drain on healthcare resources and costs



C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (**1**). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (**2**), opening of epithelial cell junctions (**3**) and epithelial cell apoptosis (**4**). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (**5**) and watery diarrhea.


ient
• Disruption of normal enteric flora
• Acquisition of toxigenic *Clostridium difficile*
40%–60%
Protective factors:
• High serum antibody response to toxin A
• Mild underlying disease
40%–60%
Risk factors:
• Low serum antibody response to toxin A
• Severe underlying disease
Asymptomatic *C. difficile* colonization (carrier state)
C. difficile diarrhea
Treatment
60%–95%
Additional protective factors:
• Age < 65 years
• No exposure to additional antibiotics
5%–40%
Additional risk factors:
• Age > 65 years
• Exposure to additional antibiotics
Low likelihood of *C. difficile* diarrhea
• May act as reservoir for nosocomial spread of *C. difficile*
Decreased risk of recurrent *C. difficile* diarrhea after treatment
Increased risk of recurrent *C. difficile* diarrhea after treatment
• 50% due to reinfection
• 50% due to relapse

Spectrum of Disease

- Most important cause of antibiotic associated diarrhoea
- Asymptomatic colonization
- Diarrhea

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

- Link with antibiotics not understood until 1978
- Testing for toxins required tissue culture – expensive and technically demanding
- Later other tests for toxin established – easier and cheaper using equipment common to most laboratories

Annual Epidemiological Commentary: Mandatory MRSA, MSSA and E. coli bacteraemia and C. difficile infection data, 2014/15

- PHE, Published July 2015
- 6.0% in C. difficile infection rate from 24.8 per 100,000 population in 2013/14 to 26.3 per 100,000 population in 2014/15
- First annual increase in C. difficile infections since the enhanced mandatory surveillance of C. difficile infections was initiated in 2007
- Overall still a big reduction of 74.5% from 2007
- Trust apportioned increase in last year= 3.6%
- Increase in non-Trust apportioned cases was greater, with a 7.5% increase over the same time period

Figure S14: Trends in rates of *C. difficile* infection (2007/08 to 2014/15)*

Fig. S14a. All reported cases rates

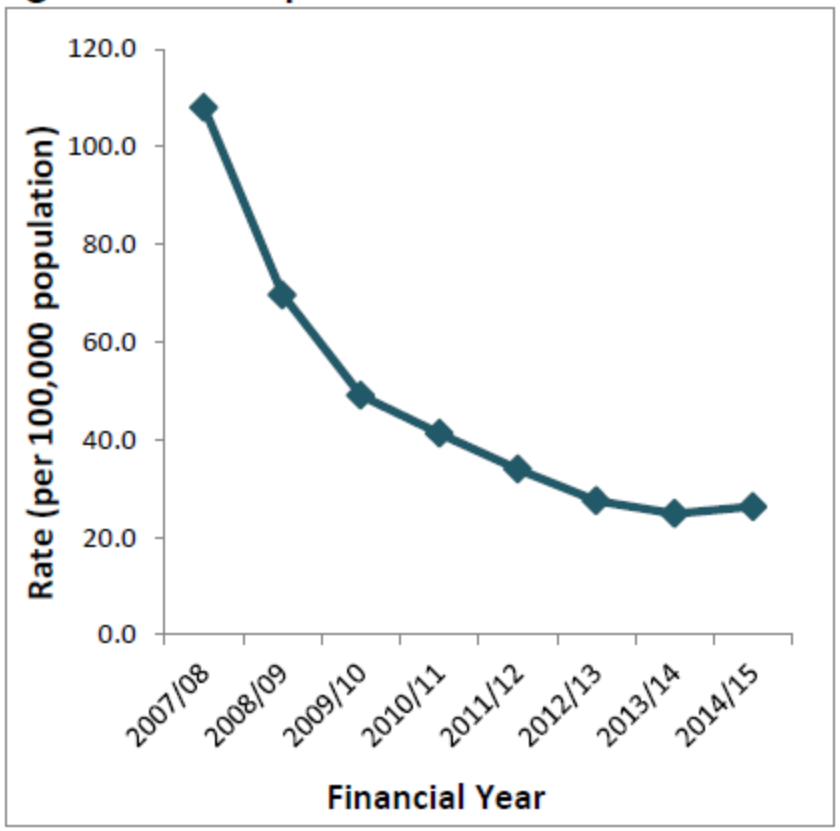


Fig. S14b. Trust apportioned rates

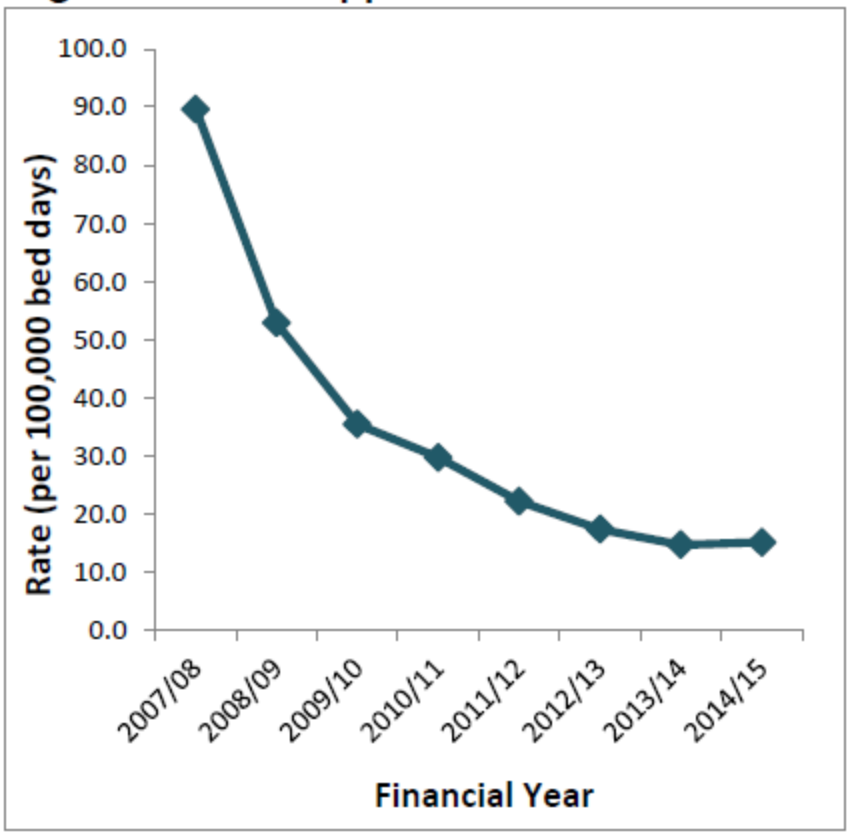


Figure S14: * FY 2014/15 population data (used in the rate calculations) had not been published at the time this analysis was performed and so 2013/14 population data were used as a proxy for 2014/15. In addition, the 2014/15 bed-day total is of an aggregate of quarter one-quarter three of 2014/15 and quarter 4 of 2013/14, as at the time this analysis was performed, quarter 4 2014/15 data had not been published

Figure 4. Age specific rates† of *C. difficile* from laboratory reports under voluntary reporting scheme: England, Wales and Northern Ireland, 2012*

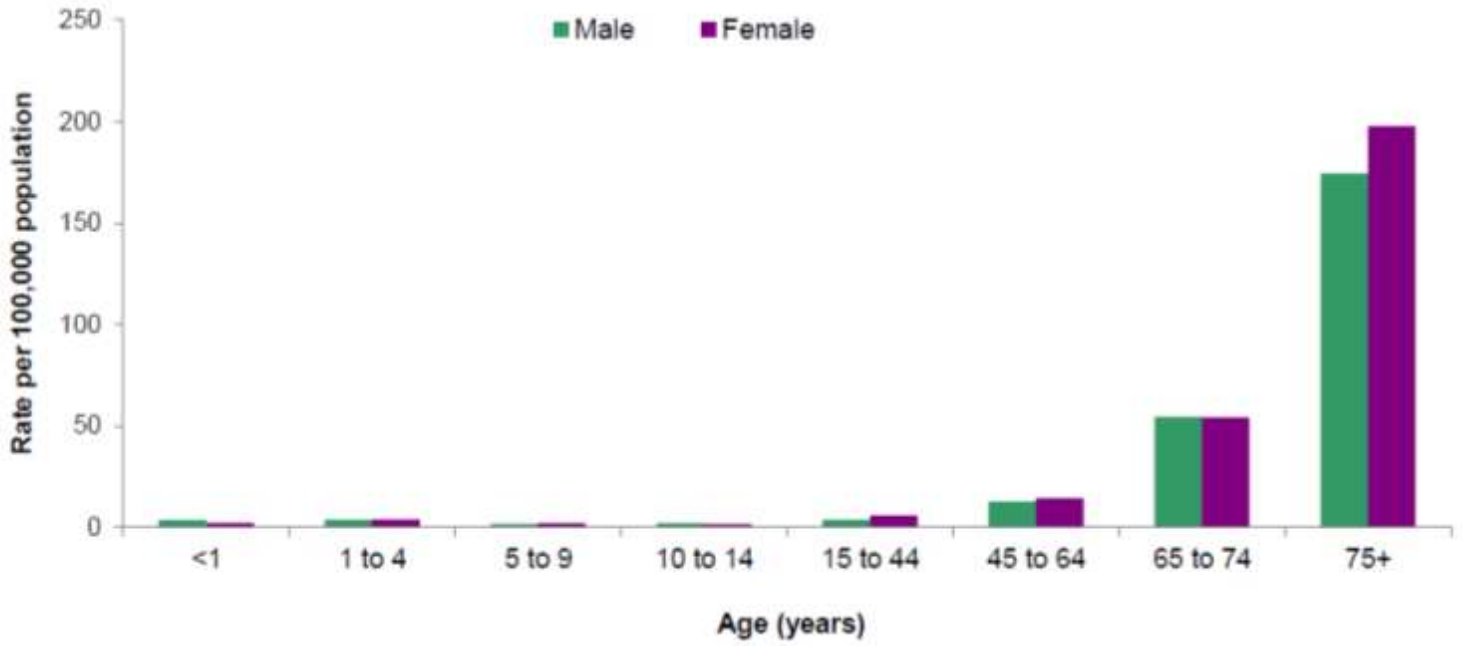


Figure S18: *C. difficile* infection rates per 100,000 population by NHS England Area Team°, 2014/15*

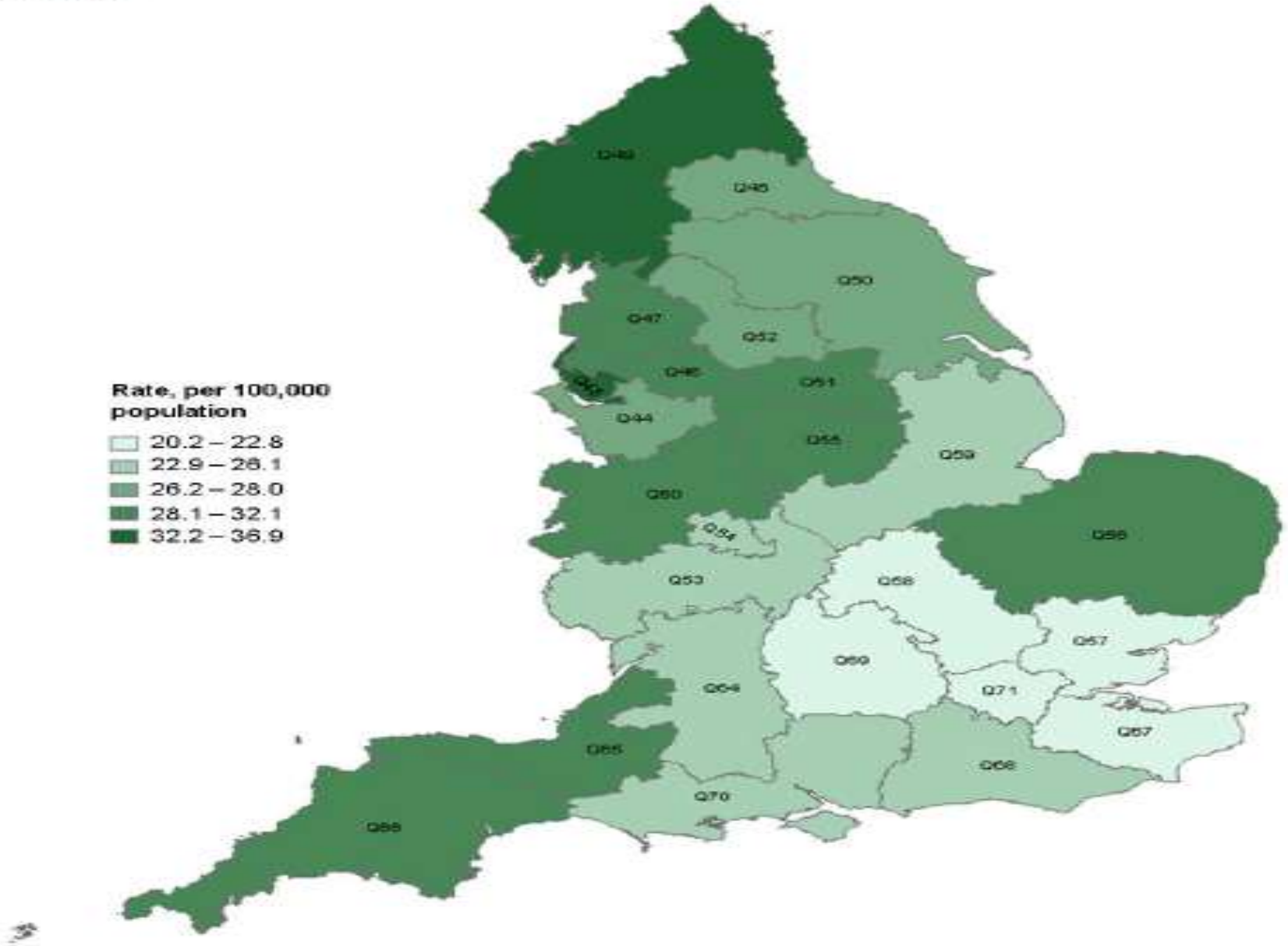


Figure S18: ° Please see Table S15 for key between Area Team codes and Area Team names
* FY 2014/15 population data (used in the rate calculations) had not been published at the time this analysis was performed and so 2013/14 population data were used as a proxy for 2014/15.

Clostridium difficile infection in Europe

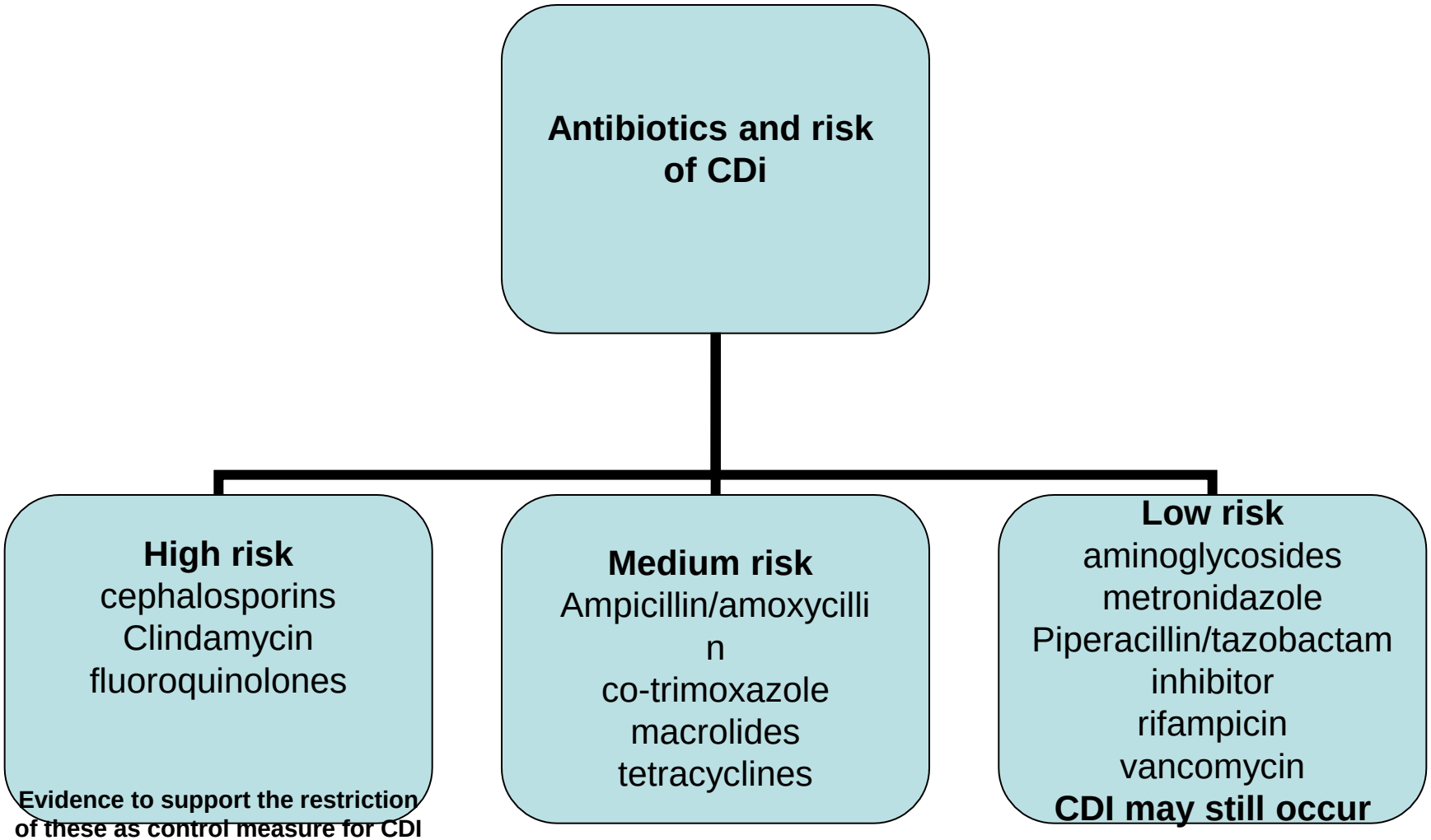
A CDI Europe Report

- **CDI is an increasing problem in the community: A**round 14% of cases of CDI tested in the ECDIS study were community-associated, i.e. they occurred in patients who had not been admitted to a healthcare facility in the previous 12 weeks.
- 10 Each year, approximately 20–30 cases of community-associated CDI occur for every 100,000 individuals in the population.
- Some recent studies in the United States suggest that community-associated CDI is becoming increasingly common.
- In the UK, CDI rates have decreased in recent years as a result of a comprehensive national intervention programme. However, the fraction of cases that were community-associated doubled from 7% in 1997/1998 to 13% in 2009/10.

- In Ireland, approximately one-fifth of CDI cases are now reported to originate in the community.
- Outbreaks of CDI have not yet been reported in the community in Europe, but this remains a possibility.
- In Australia, there was a sudden increase in community-associated CDI cases in 2011–12 caused in particular by a newly recognised strain, associated with severe infection, known as type 244.

Risk Factors

- Hospitalization, LTCFs
  - Risk increases with duration of hospital stay
- Age > 65 years
  - Neonates: High rates of *C difficile* colonization
- Antibiotic exposure
  - Cephalosporins, broad-spectrum penicillins
  - Fluoroquinolones
  - Less common with other classes
- Methotrexate
- Use of acid-suppressive therapy (controversial)
- GI surgery or GI procedures


Antibiotics and risk of CDi
High risk
cephalosporins
Clindamycin
fluoroquinolones
Evidence to support the restriction of these as control measure for CDI
Medium risk
Ampicillin/amoxycillin
co-trimoxazole
macrolides
tetracyclines
Low risk
aminoglycosides
metronidazole
Piperacillin/tazobactam
inhibitor
rifampicin
vancomycin
CDI may still occur

Recurrent CDI

- 15-20% of patients
  - Relapse
  - Re-infection
  - Post-CDI irritable bowel syndrome
- 2nd recurrence: 40%; 3rd recurrence 60%
- Rx failure before 2003 < 10%; after 2003 ~ 20%
- Relapses can continue for years
- No universal Rx algorithm

Why Do We Get Recurrent CDI ?

- Impaired host-response
- Altered intestinal microbiome
  - "Dysbiosis" = decreased microbiota diversity

Risk factors associated with recurrent *Clostridium difficile* infection (CDI). (Adapted from Eyre *et al.* [2012],

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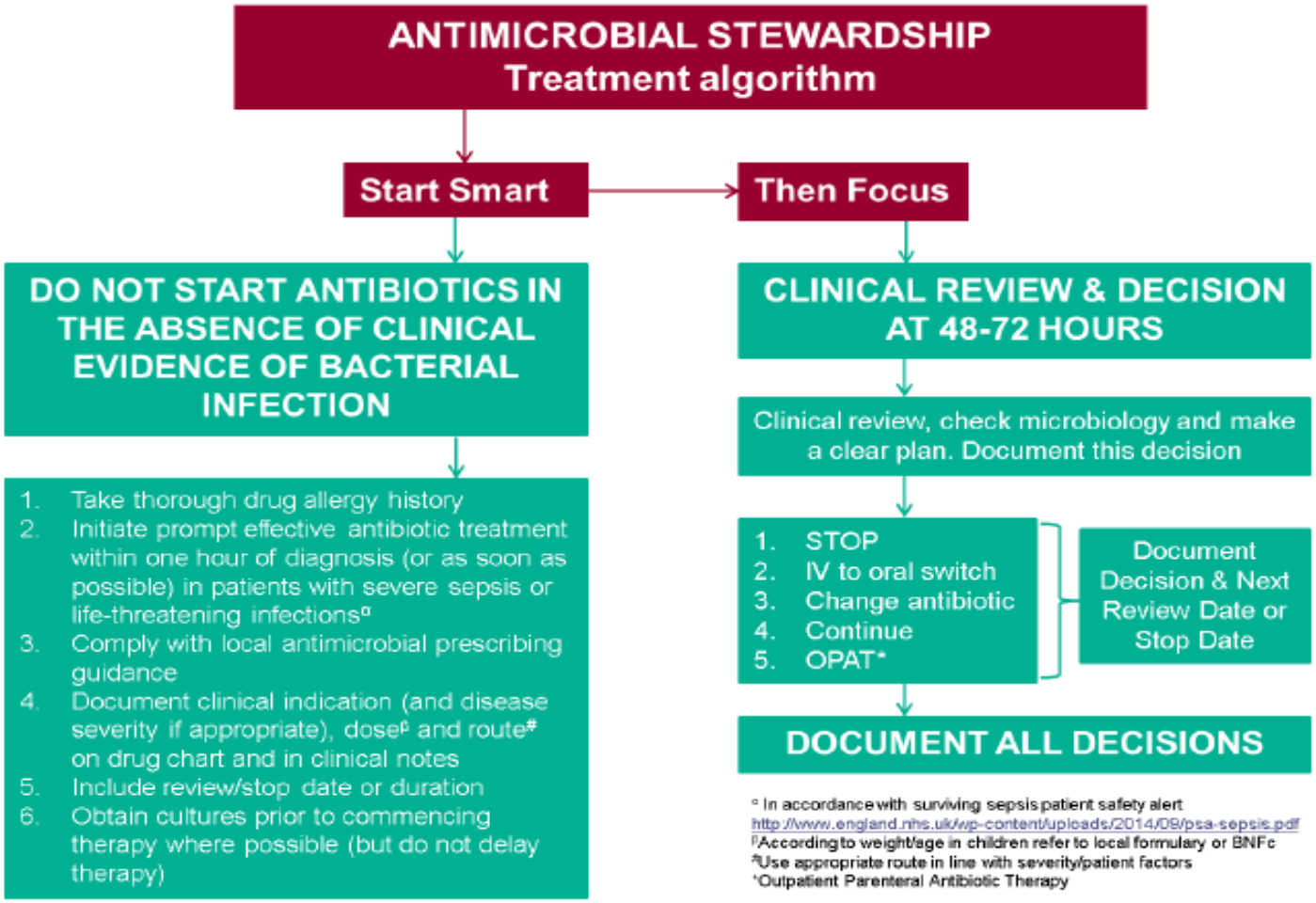
- **Altered immunity**
  - Advanced age
  - Inadequate antitoxin antibody response
  - Peripartum women
  - Leukopenia
  - Poor underlying health condition
    - Chronic renal insufficiency
    - Chemotherapy
    - Concurrent bacterial infection
    - High Horns index (score of 3 or 4)
    - Emergent hospitalization/ICU stay/prolonged hospitalization
- **Disruption of colonic flora**
  - Concomitant antimicrobial therapy, especially flouroquinolone or cephalosporin use
  - Previous episode of CDI
  - Metronidazole treatment
- **Severity of initial CDI**
  - ≥3 unformed stools
  - Hospital admission with CDI
  - Elevated C-reactive protein, elevated leukocyte count
- **Other factors**
  - (?) Proton pump inhibitors, H2 blockers, antacids

Antimicrobial Stewardship

- Systemic approach to optimising antimicrobial therapy
- Limit inappropriate antimicrobial use
- Optimise selection, dose, route and duration
- Reduce unintended consequences
  - Adverse drug reaction
  - Selection of pathogenic organisms eg Clostridium difficile
  - Emergence of antimicrobial resistance

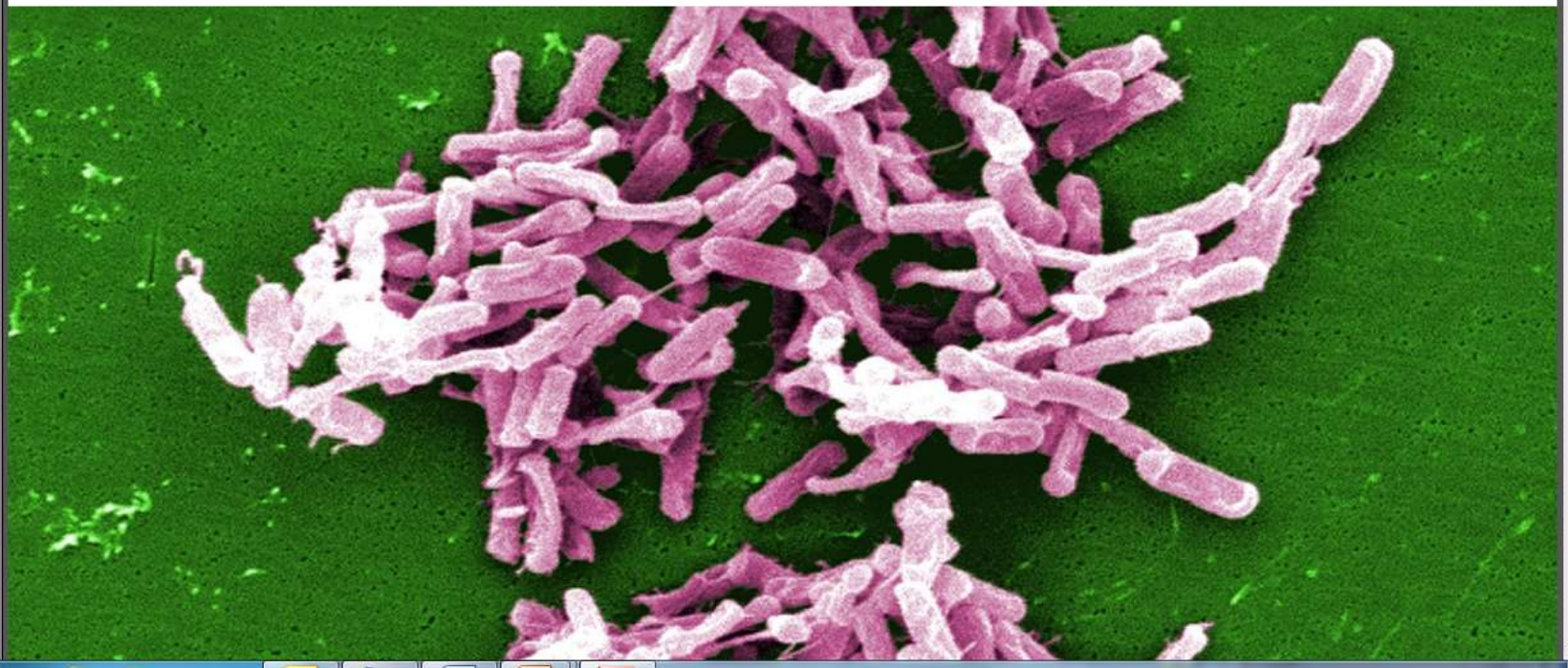
Start Smart Then Focus



Whats new with C difficile?

- Testing – Screening with GDH, Positives confirmed with Toxin EIA
- Introduced PCR for those samples that are GDH Positive and Toxin Negative or Equivocal
- PCR positivity in these cases confirms carriage/presence of a Toxigenic strain, allowing clinical assessment and prioritising infection control
- Mandatory 2 step algorithm being followed
- Those positive by both GDH and Toxin EIA are reported to the Mandatory Surveillance system

Updated guidance on the management and treatment of *Clostridium difficile* infection



Summary of new guidance……

Mild disease

- Patients with mild disease may not require specific *C. difficile* antibiotic treatment. If treatment is required, oral metronidazole is recommended (dose: 400–500 mg tds for 10–14 days) as it has been shown to be as effective as oral vancomycin in mild to moderate CDI (Zar *et al.,* 2007; Louie *et al.,* 2007; Bouza *et al.,* 2008).

Moderate disease

- For patients with moderate disease, a 10- to 14-day course of oral metronidazole is the recommended treatment (dose: 400-500 mg tds).
- This is because it is cheaper than oral vancomycin and there is concern that overuse of vancomycin may result in the selection of vancomycin-resistant enterococci (HICPAC, 1995; American Society of Health-System Pharmacists, 1998; Gerding, 2005).

Severe disease

- For patients with severe CDI, oral vancomycin is preferred (dose: 125 mg qds for 10–14 days). This is because of relatively high failure rates of metronidazole in recent reports and a slower clinical response to metronidazole compared with oral vancomycin treatment (Wilcox and Howe, 1995; Musher *et al.,* 2005; Lahue and Davidson, 2007; Zar *et al.,* 2007).
- Fidaxomicin should be considered for patients with severe CDI who are considered at high risk for recurrence; these include elderly patients with multiple comorbidities who are receiving concomitant antibiotics (Hu *et al.,* 2009; Wilcox 2012).

In severe CDI cases not responding to oral vancomycin 125 mg qds, oral fidaxomicin (200mg bd) should be considered.

Alternatively, high dosage oral vancomycin (up to 500 mg qds, if necessary administered via a nasogastric tube) plus intravenous (iv) metronidazole 500 mg tds is an option.

The addition of oral rifampicin (300 mg bd) or iv immunoglobulin (400 mg/kg) may also be considered.

Although there are no robust data to support these recommendations, the very poor prognosis may justify aggressive therapy (Abougergi *et al.,* 2011).

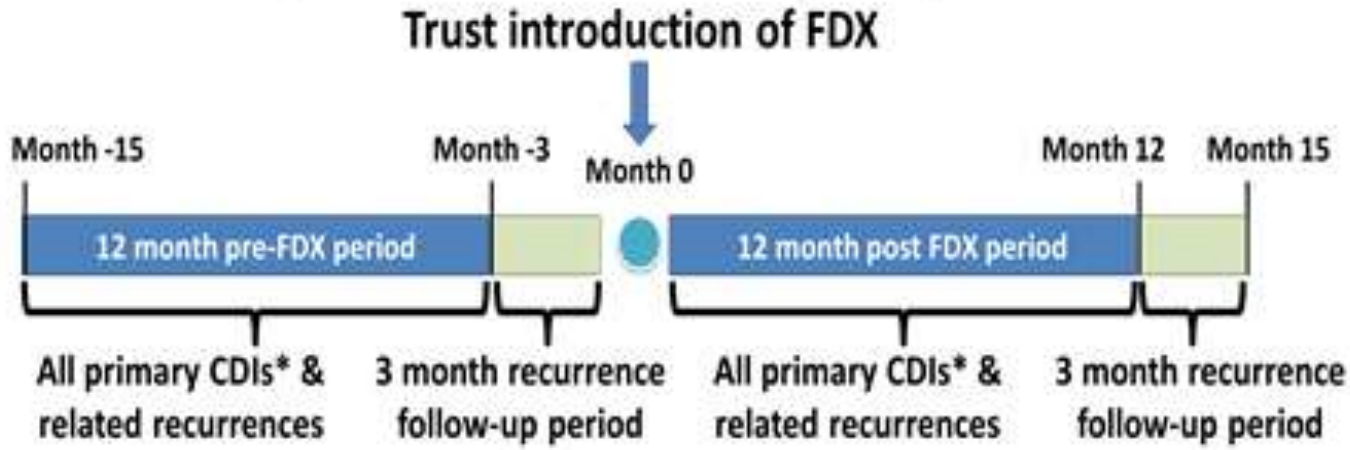
Severe (or recurrent) CDI is considered an appropriate use of IV immunoglobulin (Department of Health, 2011).

CDDFT FIDAXOMICIN EXPERIENCE

- Participated in a 7 Centre Local Service Evaluation
- Local service evaluations were conducted between Sept 2013-Sept 2014 at 7 hospitals in England who introduced FDX between July 2012-July 2013.
- All hospitalised patients aged ≥18yrs with primary CDI (diarrhoea with the presence of toxin A/B without a previous CDI in the past 3 months) were included.
- Recurrence was defined as in-patient diarrhoea re-emergence requiring treatment anytime within 3 months.
- Data were collected retrospectively from medical records (paper and electronic) on CDI episodes occurring 12 months before (Pre-FDX) and after the introduction of FDX (post-FDX), as shown in figure 1.

Design and analysis groups

Figure 1: Overview of study design



*primary CDI confirmed by absence of CDIs in previous 3 months

	Recurrence rates following primary episodes					Change pre/post		
Hospital	Pre Non-FDX	Post non-FDX	Post FDX-1st line	Post FDX-not 1st line	Post (all-treatment)	% change	Relative change	Relative change P value
A	**10.6% (7/66)**	-	3.7% (1/27)	0.0% (0/5)	**3.1% (1/32)**	-7.5%	-70.8%	ns
B	**16.3% (16/98)**	-	3.2% (2/62)	0.0% (0/2)	**3.1% (2/64)**	-13.2%	-81.0%	0.01
C	**7.7% (19/246)**	7.5% (17/227)	0.0% (0/12)	19.2% (5/26)	**8.3% (22/265)**	+0.6%	+7.8%	ns
D	**21.1% (15/71)**	9.6% (5/52)	0.0% (0/1)	66.7% (2/3)	**12.5% (7/56)**	-8.6%	-40.8%	ns
E	**12.9% (15/116)**	14.9% (7/47)	11.8% (2/17)	6.9% (2/29)	**11.8% (11/93)**	-1.1%	-8.5%	ns
F	**16.9% (15/89)**	10.0% (3/30)	9.6% (5/52)	0.0% (0/7)	**9.0% (8/89)**	-7.9%	-46.7%	ns
G	**5.4% (6/112)**	7.3% (4/55)	0.0% (0/6)	0.0% (0/8)	**5.8% (4/69)**	+0.4%	+7.4%	ns
All hospitals	**11.7% (93/798)**	8.8% (36/411)	5.6% (10/177)	11.3% (9/80)				
P value cf Pre Non-FDX		P>0.1	P<0.02	P>0.2				

Results: 28-day mortality

- In hospitals using FDX for all episodes in the post FDX period (A & B), there was a significant reduction in 28-day mortality between the pre- and post-FDX periods (fig. 2). Hospital A: $p<0.001$; Hospital B $p<0.05$.

Potential Future Therapies

- Nitazoxanide, rifaximin
- Toxin-binding polymer
  - Tolevamer
- Poorly absorbed antimicrobials
  - OPT-8 (Difimicin)
  - Ramoplanin
- Monoclonal antibodies
- *C. difficile* vaccine

Available antibiotics and investigational new agents for the management of CDI. (Adapted from Cornely [2012] and Venugopal and Johnson [2012].)

Agent	Dose	Relative efficacy	Recurrence risk	Resistance in clinical isolates	Adverse events	Comments
Fidaxomicin	200 mg po bid for 10 days	+++	+	Not reported	Abdominal pain, nausea, vomiting, anemia, neutropenia bowel obstruction and gastrointestinal hemorrhage	FDA approved for CDI; first-in-class oral macrocyclic antibiotic with targeted bactericidal activity against *C. difficile* and minimal impact on normal flora
Vancomycin	125 mg po qid for 10 days or 'taper/pulse' for recurrence: 125 mg po qid for 10–14 days, then 125 mg po bid per day for 1 week, then 125 mg po daily for 1 week, then 125 mg po every 2 or 3 days for 2–8 weeks	+++	++	Not reported	Nausea, not absorbed so systemic symptoms unlikely	FDA approved for CDI; potential for resistance induction in other clinically important pathogens (VRE)
Metronidazole	500 mg po tid for 10 days or 250 mg po qid for 10 days	++	++	Increased MICs noted in some studies	Nausea, neuropathy, abnormal taste in mouth	Not FDA approved for CDI, increased reports of treatment failures and slow response, less effective in severe CDI
Nitazoxanide	500 mg po bid for 10 days	++	++	Not reported	Nausea, diarrhea, abdominal pain	Not FDA approved
Rifaximin	400 mg po tid for 10 days or 'chaser' regimen 400 mg po bid for 14 days	++	+?	Potential for development of high-level resistance	Headaches, abdominal pain, nausea, flatulence, not absorbed	Not FDA approved for CDI, used primarily as post-vancomycin
Teicoplanin	400 mg po bid for 10 days	+++	++	Not reported	Not absorbed so systemic symptoms unlikely	Not FDA approved for CDI, similar results to vancomycin.
Tigecycline	50 mg iv every 12 hours for 10 days	++?	?	Not reported	Nausea, vomiting, diarrhea	Not FDA approved for CDI; limited case reports of

Nonantibiotic alternatives and investigational new agents for the management of CDI. (Adapted from Cornely [2012] and Venugopal and Johnson [2012].)

Agent	Comments
IVIG	Multisystemic side-effects profile. Most commonly renal failure. Efficacy for use in adults is inconclusive; in pediatrics, evidence favors efficacy.
Fecal transplantation	Infusion of feces from a healthy donor. Most evidence comes from single-center case series and case reports. A recent multicenter, long-term follow-up study has shown positive results.
Probiotics	Multiple studies favor the use of probiotics for the prevention of CDI and antibiotic associated diarrhea (Hempil *et al.* 2012; Johnson *et al.* 2012; McFarland, 2006); however, appropriately powered studies are needed to confirm these findings. Guidelines do not recommend the routine use of probiotics given the lack of definitive evidence of effectiveness and potential risk of blood stream infection.

Investigational new agents

Agent	Comments
Ramoplanin	Under investigation (phase III) for the treatment of CDI. Lipoglycodepsipeptide with spectrum activity similar to vancomycin but considerably more potent.
CB-183,315	Narrow spectrum, Gram-positive lipopeptide antibiotic in phase III: development status (Mascio *et al.* 2012; Rege *et al.* 2012; NTC 01597505; NTC 01598311).
Cadazolid	Hybrid oxazolidinone-quinolone antibiotic. Currently in phase II [ClinicalTrials.gov identifier: NCT01222702].
CDAI and CDBI	Human monoclonal antibodies against *C. difficile* toxins A and B. Phase III trials for prevention of CDI, recurrence (MODIFY I [ClinicalTrials.gov identifier: NCT01241552] and MODIFY II [ClinicalTrials.gov identifier: NCT01513239]).
ACAM-CDIFF	Active *C. difficile* toxoid vaccine. Phase II placebo-controlled for primary CDI prevention [ClinicalTrials.gov identifier: NCT00772343].
VP 20621	Nontoxigenic *C. difficile*. Phase II trial for prevention of CDI recurrence [ClinicalTrials.gov identifier: NCT01259726].

IVIG, intravenous immunoglobulins; CDAI, Human monoclonal antibody to *C. difficile* toxin A; CDBI, Human monoclonal antibody to *C. difficile* toxin B.

Ongoing Challenges


BBC NEWS KENT

Maidstone NHS trust to face £1.5m C.difficile bug fine

- Emergence of **highly virulent CD**
- **Increased incidence** of CDI
- **Increasing number of young patients** are acquiring CDI with no history of antibiotic treatment
- **Relapse of CDI** – common
- **Effective treatment** for relapse – **poorly defined**
- High number of patients with **severe CDI**
- **Rapid and accurate laboratory diagnosis** – critical – to reduce morbidity of CDI, to allow the implementation of infection control measures

Aspiration: C DIFFICILE Integrated Care Pathway for CDD Patients

- When used effectively, an appropriately developed ICP:
- • Supports multidisciplinary care
- • Encourages simple record--keeping
- • Allows locally determined standards to be set
- • Facilitates clinical audit
- • Enables variance from the normal pattern of care to be highlighted
- • Enhances communication between clinical staff, and with patients
- • Provides a structured plan for patient care

- • Describes the expected Progress for a “typical” patient
- • Outlines the normal timescale of events
- • Presents the procedures to be followed, in the right order
- • Is backed up by evidence
- • Incorporates guidelines based on best practice

- The CDI Integrated Care Pathway comprises seven forms, which are designed to cover the potential stages of a patients’ outpatient pathway.

- A joint approach to tackling HCAI within an entire health economy makes sense!
- *C difficile* identifies no barriers!
- Until we know more about the pathophysiology of C difficile, we have to do all we can – Antimicrobial Stewardship, Handwashing, Infection Control and optimal diagnosis and management!

Any Questions...
Just Ask!