Clostridium difficile infection: New Zealand perspective

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Introduction

- Historical
- Laboratory diagnosis
- Survey
  - 2009
  - 2011
- Other issues
  - RT 244
  - Paediatrics
- Infection prevention and control

History

LINCOMYCIN AS A CAUSE OF PSEUDOMEMBRANOUS COLITIS

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Summary Eight patients with pseudomembranous colitis are described. In seven of the eight the administration of lincomycin preceded the illness. Three of these patients died. An association between pseudomembranous colitis and lincomycin is supported by the frequency with which the disease has been diagnosed since the widespread introduction of the drug. This association also illustrates the role of a disturbance of gut flora in the pathogenesis of some forms of pseudomembranous colitis.

with fever, severe abdominal cramps, intestinal distention, leukocytosis and blood and mucus in the stool." In 1970, four patients in whom pseudomembranous colitis developed as a sequel to lincomycin therapy [4,5] were reported.

Pseudomembranous colitis has not, in our experience, proved to be a common condition. Yet in most cases there are distinctive rectal findings,[5] radiological studies are often striking,[6] and the gross pathological and the microscopic appearance of the lesions is always such [7] as to make it difficult to suggest that the condition was occurring unrecognised. We have therefore been impressed by the occurrence of seven cases of the condition in as many months, six of the seven occurring as a sequel to lincomycin administration, while in the seventh patient the antibiotic history is unclear. Review of the post-mortem records of the two hospitals in which these patients were seen revealed only one other patient with pseudomembranous colitis over

- *C. difficile* was identified in 1977 as the major cause of antibiotic-associated colitis

Laboratory Diagnosis

- Diagnosis
  - Culture, cell cytoxicity assay and neutralisation
  - Immunologic methods
    - Enzyme immunoassays
    - Latex agglutination
    - Immunochromatogenic assay
      - Toxin A and B
      - Antigen – glutamate dehydrogenase (GDH)
  - DNA-based assays
      - PCR
      - Loop-mediated isothermal amplification (LAMP)

Testing in NZ

- Pathology 2011; 43(5); 482-487
  - Online survey of 48 Australian and New Zealand (10) Laboratories (2008-2010)
  - Most laboratories used EIA assays to detect toxin A and B
  - 5.3% of all tests were positive
  - Testing of isolates was rare
  - Conclusions
    - Low overall rates may reflect lack of sensitivity of diagnostic testing procedures

Testing in NZ

- 2011 Survey
  - All Diagnostic Laboratories in NZ asked to contribute
  - Assays in use
    - TechLab Quick Chek Complete® Assay
    - Meridian Premier™ C. difficile GDH, Premier™ Toxins A&B or ImmunoCard® Toxins A&B and illumigene® C. difficile test

Molecular Testing

- Shift to NAAT assays
  - ↑sensitivity
  - Test a variety of genes
- ADHB
  - Screen with GDH ICT
  - All positives tested by PCR
  - Cepheid Xpert™ *C. difficile* assay
    - *tcd*B, binary toxin, and *tcd*C deletion

Xpert C. difficile

Meridian illumigene

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Brief report

Improved detection of toxigenic *Clostridium difficile* using the Cepheid Xpert *C difficile* assay and impact on *C difficile* infection rates in a tertiary hospital: A double-edged sword

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Table 1
Impact of the 2-step diagnostic algorithm on laboratory detection of toxigenic *C difficile*

	First testing period (July 2009 to June 2010)	Second testing period (July 2010 to December 2011)
Total number of specimens tested	3,100	4,006
Number of GDH-positive specimens by EIA*	473	605
Number of GDH-positive/toxin-positive specimens by EIA	145	181
Number of GDH-positive/toxin-negative specimens by EIA	328	424
Number of GDH-positive/toxin-negative specimens positive for the presence of *tcdB* by PCR†	NA	218
Overall laboratory rate of toxigenic *C difficile* detection, %	4.7	9.9

NA, not applicable.
*EIA: *C difficile* Quik Chek complete test.
†PCR: Cepheid Xpert *C difficile* assay.

Testing Patterns

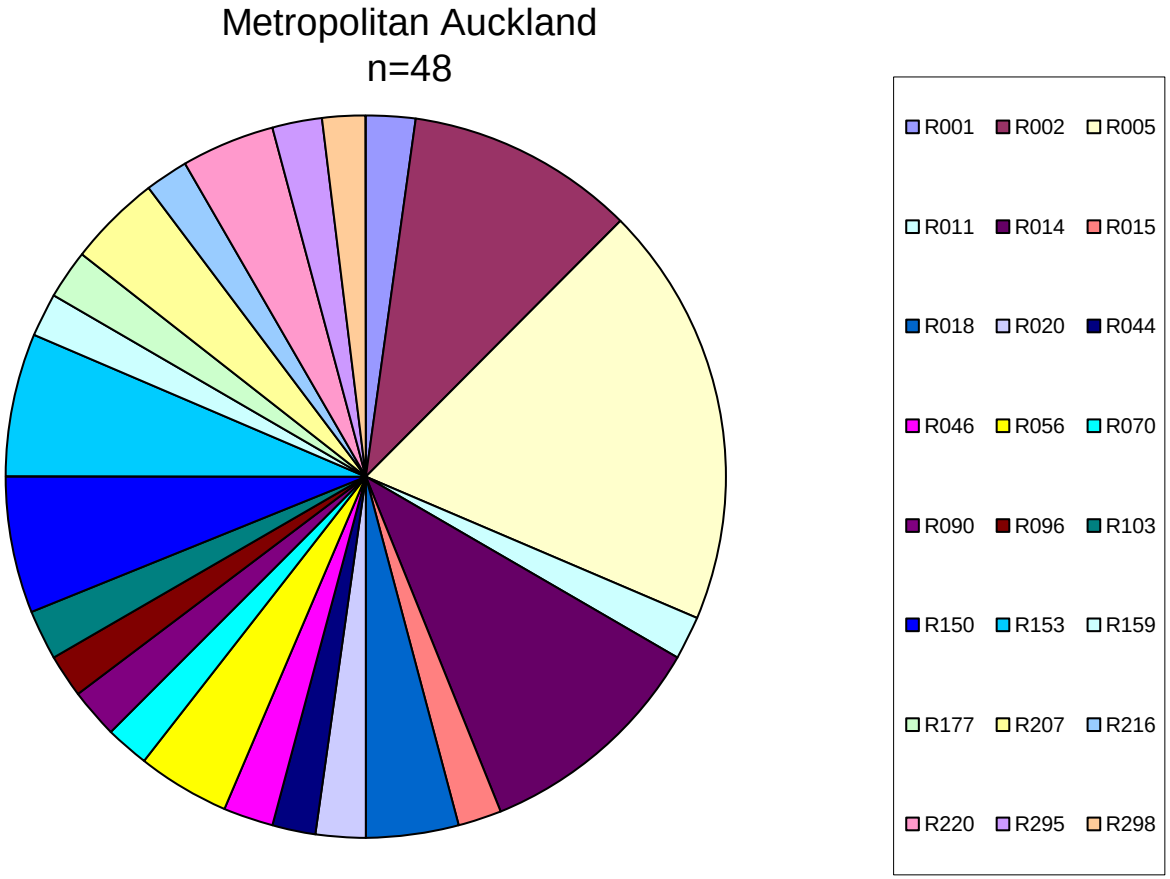
- July 2010-April 2012, specimen collected > 48 hours after admission

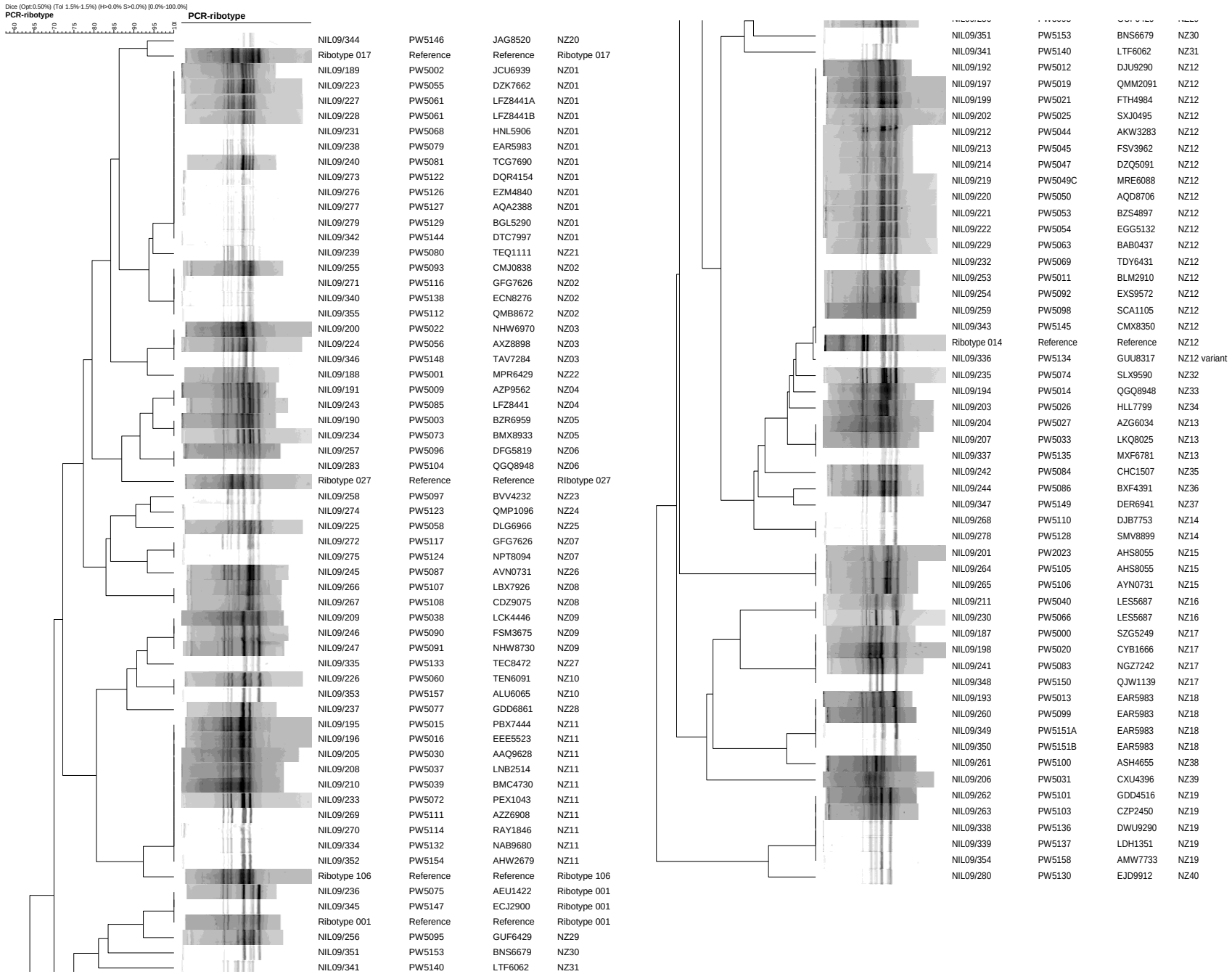
Specialty	**Number of requests**	**Number (%) positive for toxigenic *C. difficile***
General Medicine	533	35 (6.6)
Surgery/ICU	812	70 (8.6)
Haematology/Oncology	429	42 (9.8)
Liver/Renal	153	24 (15.7)
RehabPlus	113	37 (32.7)
Other	116	7 (6.0)

Epidemiology of *Clostridium difficile*

- Prior to 2009 little was know about the circulating strains of *C. difficile* in NZ
- Survey was a collaboration between ADHB and ESR
- A limited number of laboratories submitted all EIA positive stool specimens for culture at LabPlus.
- All isolates were sent to ESR for PCR-ribotyping
- Results
  - 108 isolates from 159 stool specimens or 101 isolates from 97 patients

PCR-ribotypes, n=108




Dice (Opt:0.50%) (Tol 1.5%-1.5%) (H>0.0% S>0.0%) [0.0%-100.0%]
PCR-ribotype
60 65 70 75 80 85 90 95 100
PCR-ribotype
NIL09/344 PW5146 JAG8520 NZ20
Ribotype 017 Reference Reference Ribotype 017
NIL09/189 PW5002 JCU6939 NZ01
NIL09/223 PW5055 DZK7662 NZ01
NIL09/227 PW5061 LFZ8441A NZ01
NIL09/228 PW5061 LFZ8441B NZ01
NIL09/231 PW5068 HNL5906 NZ01
NIL09/238 PW5079 EAR5983 NZ01
NIL09/240 PW5081 TCG7690 NZ01
NIL09/273 PW5122 DQR4154 NZ01
NIL09/276 PW5126 EZM4840 NZ01
NIL09/277 PW5127 AQA2388 NZ01
NIL09/279 PW5129 BGL5290 NZ01
NIL09/342 PW5144 DTC7997 NZ01
NIL09/239 PW5080 TEQ1111 NZ21
NIL09/255 PW5093 CMJ0838 NZ02
NIL09/271 PW5116 GFG7626 NZ02
NIL09/340 PW5138 ECN8276 NZ02
NIL09/355 PW5112 QMB8672 NZ02
NIL09/200 PW5022 NHW6970 NZ03
NIL09/224 PW5056 AXZ8898 NZ03
NIL09/346 PW5148 TAV7284 NZ03
NIL09/188 PW5001 MPR6429 NZ22
NIL09/191 PW5009 AZP9562 NZ04
NIL09/243 PW5085 LFZ8441 NZ04
NIL09/190 PW5003 BZR6959 NZ05
NIL09/234 PW5073 BMX8933 NZ05
NIL09/257 PW5096 DFG5819 NZ06
NIL09/283 PW5104 QGQ8948 NZ06
Ribotype 027 Reference Reference RIbotype 027
NIL09/258 PW5097 BVV4232 NZ23
NIL09/274 PW5123 QMP1096 NZ24
NIL09/225 PW5058 DLG6966 NZ25
NIL09/272 PW5117 GFG7626 NZ07
NIL09/275 PW5124 NPT8094 NZ07
NIL09/245 PW5087 AVN0731 NZ26
NIL09/266 PW5107 LBX7926 NZ08
NIL09/267 PW5108 CDZ9075 NZ08
NIL09/209 PW5038 LCK4446 NZ09
NIL09/246 PW5090 FSM3675 NZ09
NIL09/247 PW5091 NHW8730 NZ09
NIL09/335 PW5133 TEC8472 NZ27
NIL09/226 PW5060 TEN6091 NZ10
NIL09/353 PW5157 ALU6065 NZ10
NIL09/237 PW5077 GDD6861 NZ28
NIL09/195 PW5015 PBX7444 NZ11
NIL09/196 PW5016 EEE5523 NZ11
NIL09/205 PW5030 AAQ9628 NZ11
NIL09/208 PW5037 LNB2514 NZ11
NIL09/210 PW5039 BMC4730 NZ11
NIL09/233 PW5072 PEX1043 NZ11
NIL09/269 PW5111 AZZ6908 NZ11
NIL09/270 PW5114 RAY1846 NZ11
NIL09/334 PW5132 NAB9680 NZ11
NIL09/352 PW5154 AHW2679 NZ11
Ribotype 106 Reference Reference Ribotype 106
NIL09/236 PW5075 AEU1422 Ribotype 001
NIL09/345 PW5147 ECJ2900 Ribotype 001
Ribotype 001 Reference Reference Ribotype 001
NIL09/256 PW5095 GUF6429 NZ29
NIL09/351 PW5153 BNS6679 NZ30
NIL09/341 PW5140 LTF6062 NZ31
NIL09/351 PW5153 BNS6679 NZ30
NIL09/341 PW5140 LTF6062 NZ31
NIL09/192 PW5012 DJU9290 NZ12
NIL09/197 PW5019 QMM2091 NZ12
NIL09/199 PW5021 FTH4984 NZ12
NIL09/202 PW5025 SXJ0495 NZ12
NIL09/212 PW5044 AKW3283 NZ12
NIL09/213 PW5045 FSV3962 NZ12
NIL09/214 PW5047 DZQ5091 NZ12
NIL09/219 PW5049C MRE6088 NZ12
NIL09/220 PW5050 AQD8706 NZ12
NIL09/221 PW5053 BZS4897 NZ12
NIL09/222 PW5054 EGG5132 NZ12
NIL09/229 PW5063 BAB0437 NZ12
NIL09/232 PW5069 TDY6431 NZ12
NIL09/253 PW5011 BLM2910 NZ12
NIL09/254 PW5092 EXS9572 NZ12
NIL09/259 PW5098 SCA1105 NZ12
NIL09/343 PW5145 CMX8350 NZ12
Ribotype 014 Reference Reference NZ12
NIL09/336 PW5134 GUU8317 NZ12 variant
NIL09/235 PW5074 SLX9590 NZ32
NIL09/194 PW5014 QGQ8948 NZ33
NIL09/203 PW5026 HLL7799 NZ34
NIL09/204 PW5027 AZG6034 NZ13
NIL09/207 PW5033 LKQ8025 NZ13
NIL09/337 PW5135 MXF6781 NZ13
NIL09/242 PW5084 CHC1507 NZ35
NIL09/244 PW5086 BXF4391 NZ36
NIL09/347 PW5149 DER6941 NZ37
NIL09/268 PW5110 DJB7753 NZ14
NIL09/278 PW5128 SMV8899 NZ14
NIL09/201 PW2023 AHS8055 NZ15
NIL09/264 PW5105 AHS8055 NZ15
NIL09/265 PW5106 AYN0731 NZ15
NIL09/211 PW5040 LES5687 NZ16
NIL09/230 PW5066 LES5687 NZ16
NIL09/187 PW5000 SZG5249 NZ17
NIL09/198 PW5020 CYB1666 NZ17
NIL09/241 PW5083 NGZ7242 NZ17
NIL09/348 PW5150 QJW1139 NZ17
NIL09/193 PW5013 EAR5983 NZ18
NIL09/260 PW5099 EAR5983 NZ18
NIL09/349 PW5151A EAR5983 NZ18
NIL09/350 PW5151B EAR5983 NZ18
NIL09/261 PW5100 ASH4655 NZ38
NIL09/206 PW5031 CXU4396 NZ39
NIL09/262 PW5101 GDD4516 NZ19
NIL09/263 PW5103 CZP2450 NZ19
NIL09/338 PW5136 DWU9290 NZ19
NIL09/339 PW5137 LDH1351 NZ19
NIL09/354 PW5158 AMW7733 NZ19
NIL09/280 PW5130 EJD9912 NZ40

Survey 2011

- November 2011
- Funded by the Ministry of Health. Collaboration between ESR and LabPlus
- Same strategy as with 2009 survey
- Results
  - Non-duplicate isolates from 135 patients
  - Diverse range of PCR-ribotypes; 43 different RT including 32 Rt not seen in 2009

Patient Demographics

- Gender
  - Female 84
  - Male 48
- Age
  - Mean (±SD) 58 ±26 yrs
  - Median (range) 71 (2m – 100 years)
- Hospital-onset vs healthcare associated
  - 54 (42%) of patients had been in hospital > 48 hours when specimen collected
  - 55/73 (75%) hospitalised in last six months (via NMDS)

“Hypervirulent” strains?

- 2009 survey -one patient from South Island with RT 078
- 2011 Survey
  - Post Rugby World Cup
  - RT 027 in Australia

Severe infection with *Clostridium difficile* PCR ribotype 027 acquired in Melbourne, Australia

Michael Richards, James Knox, Briony Elliott, Kate Mackin, Dena Lyras, Lynette J Waring and Thomas V Riley

We report the first recognised case of infection with Clostridium difficile *PCR ribotype 027 acquired in Australia. This pathogen has caused significant morbidity and mortality in widespread hospital-based outbreaks in the northern hemisphere. Clinicians need to be aware of the clinical picture, limitations of diagnostic tests, availability of further testing for epidemic strains, new therapeutic approaches, and in-hospital control strategies for this infection.* (MJA 2011; 194: 369-371)

THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

Epidemic strains of *Clostridium difficile* are present in Auckland, New Zealand

NZMJ 15 April 2011, Vol 124 No 1332; ISSN 1175 8716
URL: http://www.nzma.org.nz/journal/124-1332/4625/

Age (years) and Gender	Comorbidities	Recent antibiotic use*	Diagnostic test^	Minimum inhibitory concentration (mg/L)#	Strains§	Disease severity and outcome
72 Female	Pancreatitis secondary to gallstones	Amoxicillin/ clavulanate	EIA and PCR	moxifloxacin >32, clindamycin >32	PCR-ribotype027	Diarrhoea resolved after treatment with metronidazole
24 Female	Chronic respiratory illness with bilateral lung transplant	Ciprofloxacin, co-trimoxazole and azithromycin	EIA	moxifloxacin 1.0, clindamycin 1.0	PCR-ribotype078	Recurrent diarrhoea, this episode resolved after treatment with metronidazole followed by vancomycin

Other current issues

RT 244

- ‘New strain’ in Australia, PCR-ribotype 244
- False-positive ‘presumptive O27’ with GeneXpert testing
- Associated with severe community-onset disease
- 2 deaths over short period of time

RT 244

- Case-control study
- Compare risk factors, disease severity and clinical outcome of CDI due to RT 244 with other strains
- To further characterise RT 244 isolates
  - Antibiotic susceptibility testing
  - Binary toxin gene PCR and *tcdC* gene sequencing

- Patients
  - **Cases:**
    - Patients from Auckland region with CDI due to RT 244
    - Oct 2011 – May 2012
  - **Controls:**
    - Patients from Auckland region with CDI due to other ribotypes.
    - Isolate included in Nov 2011 national *C. difficile* survey.
  - **Matching**
    - Controls matched 1:2 for age (± 10 yrs) and gender.

Results

- Cases (10)
  - Age, median (range)
    - 71 years (43-93)
  - 70% > 65 years
  - 50% male
- Controls (20)
  - Age, median (range)
    - 71 years (43-94)
  - 65% > 65 years
  - 50% male

- No difference in co-morbidity, antibiotic exposure, PPI use or chemotherapy
- RT 244 strains all had binary toxin and 1 bp deletion in *tcdC* gene at position 117 117
- RT 244 strains susceptible to moxifloxacin

	Cases (n=10)	Controls (n=20)	OR (95% CI)	P value
Community-associated CDI	5 (50%)	3 (15%)	5.67 (0.76-48.23)	0.078
Severe disease (ESCMID)	7 (70%)	4 (20%)	9.33 (1.27-82.59)	0.015
Treatment				
Vancomycin	2 (20%)	0	-	0.103
Surgery	0	1 (5%)	-	1.000
Outcome				
Recurrence	4 (40%)	3 (15%)	3.78 (0.49-31.85)	0.181
30 day mortality	1 (10%)	3 (15%)	0.63 (0.02-8.9)	1.000

Key points

- Newly recognized strain causing severe community-onset CDI in Australia and New Zealand.
- Ongoing surveillance of RT 244 essential to allow early recognition and intervention if necessary.
- CDI should be considered in the differential in adult patients presenting with severe community-onset diarrhoea.

CDI and children

- Children are considered at low risk of *C. difficile* infection?
- Until recently testing is not recommended in those < 2years of age.
- However, recent reports suggest that this is not the case
  - Diarrhea etiology in children presenting to ED. CID 2006;43:807-13
  - CDI amongst hospitalised children EID 2010;16:604-8

CDI in hospitalised children in Auckland

- Prospective cross sectional study of hospitalised children, Nov 2011- June 2012
- Starship Children's Hospital and Kidz First Hospital
- *C. difficile* testing was carried out on all stool specimens sent for testing on hospitalised children
- SHEA/IDSA definitions were used
- Patient demographics, illness characteristics, co-morbidities, recent healthcare exposure and antibiotic use
- Testing = EIA for GDH and Toxin A and B and PCR
- All positive stools cultured for *C. difficile*

Results

- Non-duplicate specimens from 320 children
  - 299 from SSCH and 21 from Kidz First
  - 50 positive for *C. difficle*
    - 33 HA-CDI
    - 17 CO-CDI

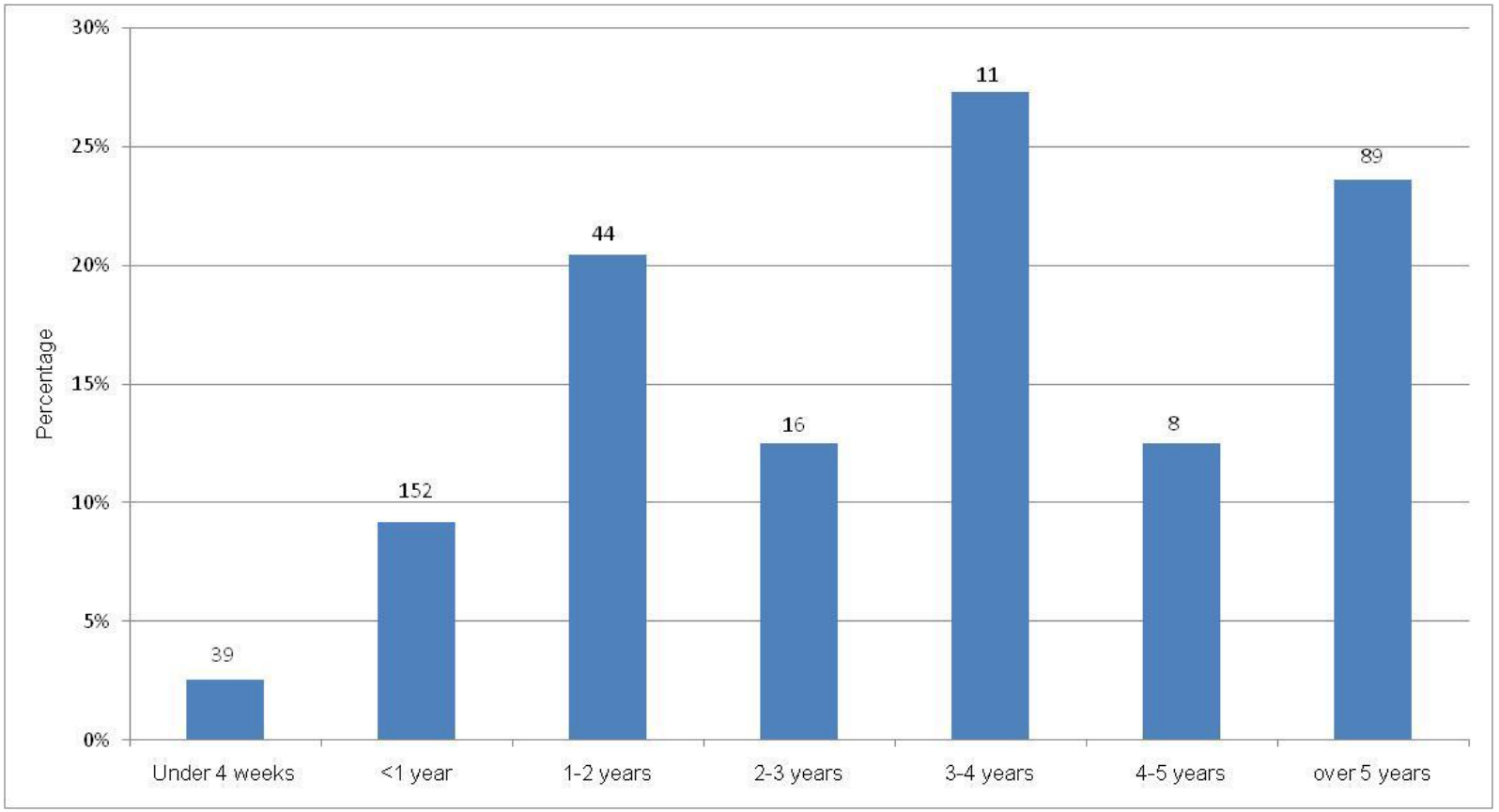
	Cases N=50 (%)	Controls N=270 (%)	p	Odds Ratio (95% CI)
Age Median (range)	5 yrs (9 days to 15 yr)	3 yrs (3 days to 15 yr)		
Gender:				
Male	31 (6)	160 (59)	0.76	1.12 (0.58-2.19)
Female	19 (38)	110 (41)		
Ethnicity:			0.008	
NZ European	30 (60)	101 (37)		
Māori	7 (14)	57 (21)		
Pacific	4 (8)	67 (25)		
Other	9 (18)	45 (17)		

Results

- No difference in symptoms, antibiotic usage
- Receipt of gastric acid suppressive Rx and chemotherapy significantly associated with CDI
- Microbiology
  - 87% tested for other pathogens; 4 cases (8%) and 28 controls (10%) had another pathogen identified
  - 37/50 patients had *C. difficile* isolated and 23 PCR-RT identified. RT 014 most common

Results

% of patients with a positive test stratified by age



Conclusions

- *C. difficile* is a common cause of healthcare-associated diarrhoea in children also
- Similar risk factors to adults
- Low rates in neonates
  - ? Due to improve IPC practices

Infection prevention and control

Issues

- Transmission-based precautions
- Hand hygiene
  - Soap and water vs alcohol-based hand rubs
- Surveillance
  - Notification to IPC Service
  - Hospital-wide surveillance

Hand Hygiene

- Soap and water more effective against the spores than ABHR
- Rates of CDI have not increased in centres that use ABHR
- Rates of VRE, MRSA and ESBL have been shown to decrease with increased use of ABHR but not with soap and water
- Outbreak vs non-outbreak approach

Surveillance for CDI

Surveillance

- Laboratory surveillance
  - Number of positive tests per month
- Clinical surveillance
  - Population-based
  - Hospital rates
    - Healthcare-associated
    - Community-onset healthcare-associated

Clinical Surveillance

- Definitions
  - SHEA/IDSA
  - England, Wales and Northern Ireland
    - Laboratory notification
    - Reported per 100,000 population
  - Scotland
    - Rate per NHS Board
  - Australia
    - VICNISS
    - Australian Commission on Safety & Quality in Healthcare

SHEA/IDSA

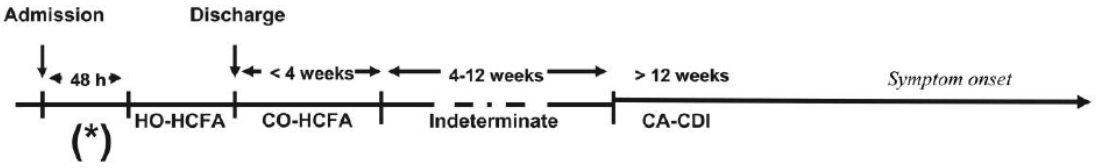


FIGURE 1. Time line for surveillance definitions of *Clostridium difficile*–associated infection (CDI) exposures. A case patient who had symptom onset during the window of hospitalization marked by an asterisk (*) would be classified as having community-onset, healthcare facility–associated disease (CO-HCFA), if the patient had been discharged from a healthcare facility within the previous 4 weeks; would be classified as having indeterminate disease, if the patient had been discharged from a healthcare facility within the previous 4–12 weeks; or would be classified as having community-associated CDI (CA-CDI), if the patient had not been discharged from a healthcare facility in the previous 12 weeks. HO-HCFA, healthcare facility–onset, healthcare facility–associated CDI.

- Numerator = case symptoms and positive laboratory diagnosis or PMC on endoscopy or histology
- Denominator = patient days
- Rate = cases per 10,000 patient days

England, Wales and Northern Ireland

- Mandatory reporting for patients >65 yrs from Jan 2004
- Expanded to include all >2 - 64 years in April 2007
- Numerator = lab reports
- Denominator = population
- Rate = lab reports per 100,000 population

Scotland NHS

- Numerator = number of CDI cases
- Denominator = population in Board area
- Rate = cases per 100,000 total occupied bed days
- Report for patients ≥ 65years and for 15-64 years

Australia

- VICNISS
  - Numerator = patient episodes of healthcare associated CDI*
  - Denominator = occupied bed days
  - Rate = cases per 10,000 OBD
- Australian Commission
  - Numerator = patient episodes of hospital-identified CDI
  - Denominator = total patient days
  - Rate = cases per 10,000 patient days

* SHEA definition

New Zealand

DHB	Defn	Numerator	Denominator	Rate	Actual rates
CMDHB	Australian	HA-CDI case	Patient days	HA-CDI cases /1000 patient days	0.22/1000
CDHB	IDSA/SHEA	Positive tests/cases	Patient days	Cases/1000 patient days	0.05-0.45/1000
WDHB	Australian	Positive tests/cases	Bed days	Cases/10,000 bed days	NSH-7.4-6.7 Waitakere 8.6-7.9/10,000
CCDHB	?	Positive test/cases	OBD	Cases/100,000 occupied bed days	5.3/100,000
ADHB	IDSA/SHEA	Positive tests/cases	Patient days	Cases/10,000 patient days	
Laboratory-based					
Hawkes Bay DHB		Positive tests	Month	Postive test/month	
Wairarapa DHB		Positive tests	Month	Positive test/month	
SDHB		Positive tests	?		
CCDHB		Positive tests	Month	Positive test/month	
BOP and Lakes		Positive tests	Month	Positive test/month	Use Control Chart

Issues

- Which definition to use?
- Hospital onset vs healthcare-associated vs community onset
- Use of NMDS to assist with applying surveillance definition
- Need to standardise the laboratory testing strategy so rates are comparable.

Acknowledgements

- ESR
  - Helen Heffernan
  - Sarah Bakker
- Department of Microbiology, ADHB
  - Nadia Al Anbuky
  - Terri Swager
  - Anne Dervan
- Dr Mary De Almeida
- Dr Vani Sathyendran
- Prof Tom Riley
- Dr. Joshua Freeman
- Dr Deborah Williamson
- Dr. Susan Taylor (CMDHB)
- Dr. Hasan Bhally (WDHB)