THE NORTHERN HOSPITAL

CLOSTRIDIUM DIFFICILE INFECTION

"Woman with a Parasol in a Garden", oil on canvas, 1875, Auguste Renoir

Early this century the members of the Explorers Club of New York faced a shrinking supply of unclimbed mountain peaks, unwalked polar ice sheets, and unvisited Amazonian tribes. In 2009 they adapted by adding biodiversity to their purview, which turned out to be a wise choice. The exploration of biodiversity offers scientists and adventurers alike the greatest physical adventures that remain on planet Earth.

Remarkably, the new emphasis on biodiversity includes an auspicious examination of the flora and fauna inhabiting our own bodies. The ability to rapidly sequence the DNA of microorganisms has revealed that each healthy person contains a series of balanced ecosystems composed primarily of bacteria. Like microbes resident in other organisms, they are mostly friendly to their human hosts. Called "mutual symbionts" by biologists, they both benefit from the plants or animals with whom they live, and give benefit in return.

Over five hundred such species of bacteria live in the mouth and esophagus of the average human. By forming a well adapted microbial rain forest, they protect this part of the body from harmful, parasitic species of bacteria. The price of failure in the symbiosis is an invasion of aliens, the buildup of dental plague, tooth decay, and gum disease.

Farther down in each successive part of the gastrointestinal tract, colonies of other specialized bacteria play crucial roles in digestion and waste disposal. The average number of human cells in the body runs at least into the tens of trillions - one number calculated from multiple estimates is forty trillion. The average number of bacteria in our microbiome, as it has become to be called, is at least ten times higher. To make the point, microbiologists joke that if biological taxonomy were to be based exclusively on the preponderance of DNA within each organism, human beings would be classified as bacteria.

It should not be surprising to learn that the microbiome looms large in medical science and practice. Researchers have come increasingly to investigate the symbionts' role in a wide range of health problems, usually those arising in the gastrointestinal tract but also including obesity, diabetes, proneness to infections, and even some forms of mental illness. The microbiome is an interlocked array of ecosystems whose species need to be kept diverse and in correct balance. In a nutshell, much of future medical practice will become a kind of bacterial gardening.

The gardens growing within human beings and other animals are typical of complex ecosystems everywhere, inside and out. The overall number of kinds of microbes dwelling in animals and plants worldwide remains entirely unknown, but it must be enormous. Those inhabiting wood-eating termites, microbiologists have found, are drastically different from the ones carried by carnivorous ants, and so on a fortiori to other organisms as diverse as frogs and earthworms. It is obvious that symbiotic microbiology, which encompasses these systems, has emerged as an exciting frontier of science, and will remain so for decades to come.

Edward O. Wilson, "Half-Earth", W.W Norton 2016.

The magisterial Edward O. Wilson, uses the charming analogy of a healthy garden being dependent upon the health of its complex symbiotic ecosystems to explain the critical importance of the microbiome to our own health. Just as finally tuned ecosystems, evolved over untold eons of time, may be devastated by the unthinking use of chemical pesticides, or the introduction of non-native species, so may we devastate the ecosystem of our gastrointestinal tracts with the use of antibiotics. This may severely upset the delicate balance of symbionts, leading to an unnatural preponderance of dangerous organisms such as toxin producing strains of clostridium difficile.

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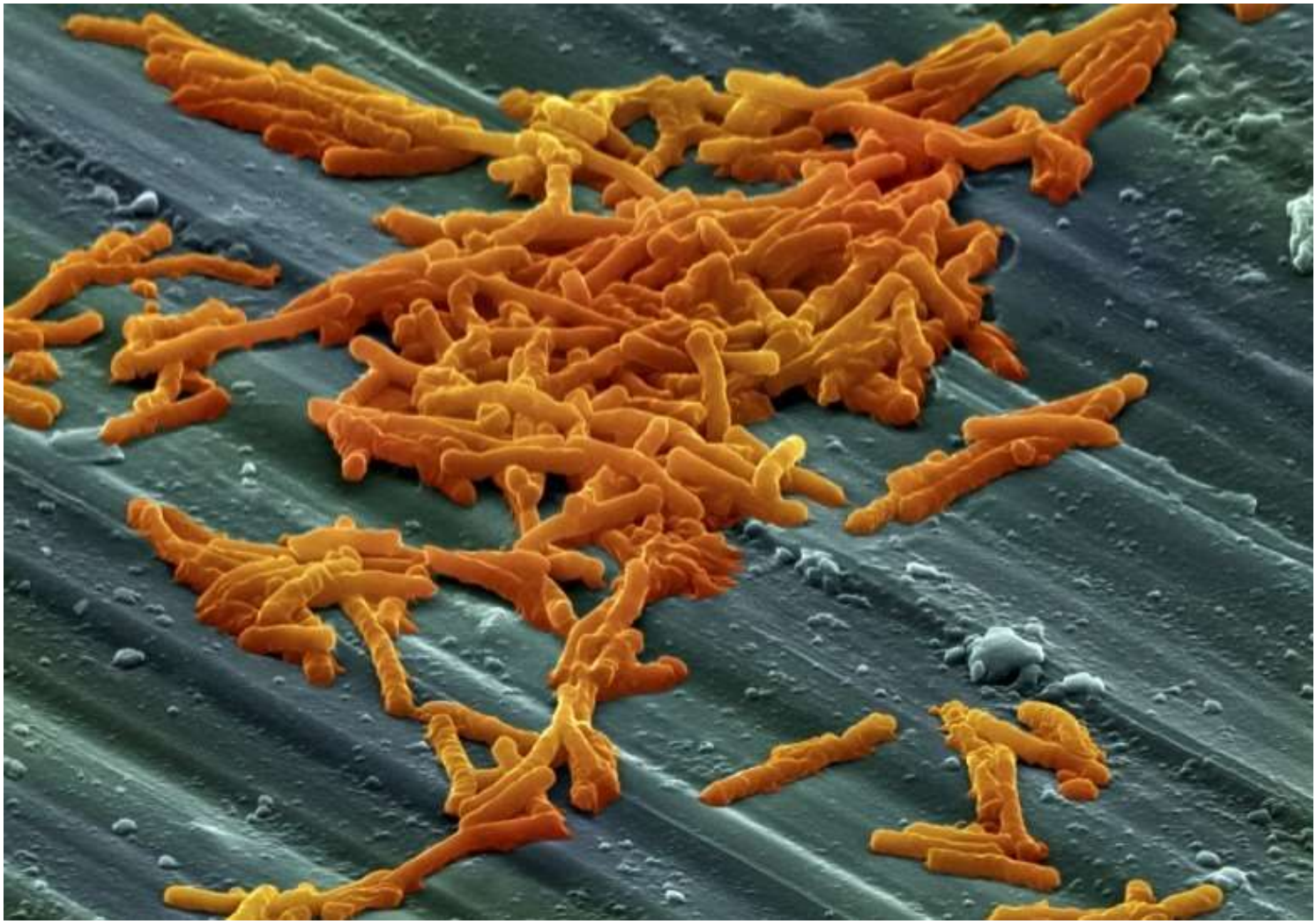

A colour-enhanced scanning electron micrograph image showing a cluster of Clostridium difficile, (Annie Cavanagh, Wellcome Images; www.cellimagelibrary.org/)

Introduction

Clostridium difficile infection (CDI) is the most common cause of nosocomial and antibiotic associated diarrhea.

The severity of infection varies from mild diarrhoea to pseudomembranous colitis to toxic megacolon and death.

Recently a new **hypervirulent strain - PCR ribotype 027** – has emerged in Europe and the USA. This strain has increased morbidity and mortality and has now been isolated in Australia, the first case occurring in WA in 2009.

Vigilance and a high index of suspicion must me maintained for this emerging disease.

Epidemiology

Recently a new **hypervirulent strain - PCR ribotype 027** – has emerged in Europe and the USA. This strain has now been isolated in Australia, including Melbourne.

In general terms CDI should be suspected in:

- Elderly patents in nursing homes.
- Hospitalized patients of > 48 hours who develop a diarrheal illness.
- Any person in the community who develop diarrhea after antibiotics, especially or in association with immunosuppressive therapy or conditions.

Pathology

Organism

Clostridium difficile is a gram-positive, anaerobic, toxigenic bacterium.

It exists in both vegetative and **spore** forms.

Two main toxins are produced, type A and type B.

PCR ribotype 027 is a new hypervirulent strain which is characterised by:

- Increased resistance to fluoroquinolones
- Increased toxin production
- Increased sporulation
- Increased morbidity and mortality.

Mechanism of disease

In healthy people, *C. difficile* does not cause problems; resistance to infection is thought to be due in part to commensal bowel flora and antibody-mediated immunity.

Impairment of the normal resistance mechanisms, including disruption of host flora by most antibiotics, gastric acid suppression, immunosuppression or cytotoxic drugs may result in *C. difficile* colonising the gastrointestinal tract.

For reasons that are not well understood, a proportion of colonised individuals progress to *C. difficile* infection (CDI) following overgrowth of toxin-producing strains of *C. difficile.*

Risk factors:

Risk factors for CDI include:

1. Antibiotics
2. Gastric acid-suppressive therapy
3. Elderly
4. Prolonged hospitalisation
5. Immunosuppression:
    - Cancer chemotherapy
    - Significant comorbidities

Complications

The emerging hypervirulent strain - **PCR ribotype 027 -** has increased morbidity and mortality.

Pseudomembranous colitis and toxic megacolon are seen.

Death can result from hypovolemic, or septic shock.

Incubation Period

CDI usually occurs 5 to 10 days after commencing antibiotic therapy, although symptoms have been described as early as 2 days and as late as 10 weeks after antibiotic treatment.

Transmission

Current theory holds that colonisation of the hypervirulent strain is spread between patients via fecal/oral route, and then treatment with antibiotics precipitates the diarrhoeal illness, which is more severe with the hypervirulent strain. There are sporadic cases that haven't had antibiotics but most have had them.

Of particular concern is the potential for hospital outbreaks, and standard infection control precautions are essential to minimise this risk.

Clinical Features

In general terms CDI is characterized by:

1. Fever
2. Nausea, anorexia, abdominal pains.

3. Watery diarrhoea is usual but may occasionally be bloody.

The Australasian Society for Infectious Diseases has provided more precise case definitions:

CDI

- Clinical features of CDI (diarrhoea, ileus, toxic megacolon)

AND

- Microbiological evidence of toxin-producing *C. difficile*

OR

- Pseudomembranous colitis on colonoscopy

Severe CDI

Any of the following features are suggestive of severe CDI:

1. Clinical features:
    - Fever (>38.5°C), rigors
    - Haemodynamic instability
    - Peritonitis or evidence of bowel perforation
    - Ileus or toxic megacolon
2. Blood tests:
    - White blood cell count >15 x 10^9/L and < 20% neutrophils
    - Elevated lactate level
    - Rise in creatinine level (> 50% above baseline)
    - Albumin level < 25mg/L
3. Plain radiography/ CT scanning:
    - Large intestine distension, colonic wall thickening, fat stranding, unexplained ascites.
4. Colonoscopy:

- Pseudomembranous colitis

Treatment failure

- Lack of improvement or increasing stool frequency after 3 days of treatment
- New signs of severe CDI

Recurrence

- Increasing stool frequency over 2 consecutive days

OR

- New signs of severe CDI after apparent improvement

Re-testing of patients is generally not helpful as colonisation may persist for some weeks.

Investigations

Any inpatient in hospital for > 48 hours, who develops diarrhea, should be screened for CDI

Blood tests

1. FBE
    - Elevated WCC in about 40% of cases.
2. CRP
3. U&Es/ glucose
4. LFTs
    - Hypoalbuminaemia is seen in about 76% of cases.
5. Lactate
    - Elevated levels correlate with more severe disease.
6. Venous blood gases

Stool microbiological studies:

The following may be done:

1. For clostridium difficile culture and **toxins**

- The **toxin** itself must then be tested for as there are strains of clostridium difficile which are not toxin producing.

2. **PCR testing**

3. Enzyme immunoassays detecting *C. difficile* glutamate dehydrogenase, and/or toxin A and/or B.

Contact the laboratory and ID specialist regarding any additional studies to test for **hypervirulent strains** in patients who develop severe CDI

Plain radiography AXR:

Radiological evidence of dilatation of the large bowel without involvement of the small bowel, thickening of the bowel wall or perforation indicates severe disease.

Abdominal Ultrasound

This is not a routine test but is useful to document suspected ascites (which is associated with hypoalbuminaemia). If confirmed this is suggestive of severe CDI

Colonoscopy

Looking for the characteristic macroscopic changes of pseudomembranous colitis.

Tissue samples showing the histological characteristic features of pseudomembranous colitis.

The presence of pseudomembranes on colonoscopy is an indicator of severe disease.

Management

1. IV Fluid resuscitation as clinically indicated.

2. Correction of any electrolyte disturbances.

3. Isolation room and full barrier nursing, as per local hospital guidelines.

4. Where possible, therapy with the initiating antibiotic should be ceased

5. Antiperistaltic agents and opiates should be **avoided.**

6. Metronidazole:

   To treat an initial episode and a first recurrence, **metronidazole** is the preferred antibiotic, with **oral vancomycin** reserved for *severe disease* and *subsequent recurrences.*

   Give:

- **Metronidazole, 400 mg orally, three times daily for 10 days**

In patients with colitis, adequate metronidazole concentrations in the colon are similar after oral and intravenous administration. Hence, if tolerated, the oral route is preferred.

- If unable to tolerate oral treatment:

  Some recommendations are for IV metronidazole, however there is not uniform agreement on this and so this scenario should be discussed with the Infectious Diseases physician.

7. Vancomycin:

Vancomycin is reserved for *severe disease* and *subsequent recurrences.*

Vancomycin is not absorbed after oral administration, and much higher gastrointestinal concentrations are achieved when it is given orally rather than intravenously, whereas concentrations of metronidazole given by either route are low in stool.

Give:

- **Vancomycin, 125 mg orally, four times daily for 10 days**

If unable to tolerate oral therapy: one option includes:

- **Metronidazole 500 mg intravenously, 8-hourly for 10 days**

PLUS

A retention enema of **vancomycin, 500 mg in 100 mL of normal saline every 4 - 12 hours** and/or **vancomycin, 500 mg four times daily by nasogastric tube.**

Again however there is not uniform agreement on this approach and this scenario should also be discussed with the Infectious Diseases physician.

8. Surgery:

Surgery should be considered for fulminant disease.

The following are indications for surgical review:

- Bowel perforation.

- Toxic megacolon

- Deterioration (including *severe ileus*, rising lactate level, rising white cell count, ongoing severe sepsis) despite antibiotic treatment.

References

1. Allen C Cheng, John K Ferguson et al. Australasian Society for Infectious Diseases guidelines for the diagnosis and treatment of *Clostridium difficile* infection. MJA, 4 April 2011, Vol 194 no. 7, p. 353-358.

2. eTG - March 2017

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