The rising menace of toxic enterocolitis of Clostridium difficile et al
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Discussion
A recent "hyper virulent" Quebec strain of C. difficile is linked to abuse of antibiotics, primarily in industrial animal feeding operations (factory farms). The mutation from originally quite benign bacteria to hyper virulent strains, under the influence of exposure to antibiotics, is evident in the invasive toxin producing E. coli 0157:H7 strain which spreads from manure reservoirs to the general public via contaminated water, or farm produce. The potential exists for other deadly Clostridia (C. septicum, C. perfringens, C. botulinum and C. tetani) to become more invasive and more lethal than the toxin-producing ulcerative enterocolitis that they already produce.

There is already a link between infantile Clostridium botulinum enterocolitis and sudden infant death syndrome (SID). Endemic infections in factory farms (E. coli, C. difficile, C. perfringens and MRSA) are well known to veterinarians and factory farm operators, but the general public are (intentionally) kept unaware of this. C. difficile is one of the Clostridium genus pathogens which incudes, C. difficile, C. perfringens, C. septicum, C. botulinum, C. butyricum and C. tetani. These gram positive spore-forming anaerobic rods, most of which are motile (by flagellae), increase their deadly invasiveness by producing potent toxins, two of which are among the world's most lethal - the toxins of botulism and tetanus.

As the antibiotic era dawned, Alexander Fleming, in his 1945 Nobel laureate address, "Penicillin" (Ref. 1), warned that "the ignorant man", in his "negligent use" (at low doses) of an antibiotic that "could be bought by anyone at the shops" without a prescription could "change the nature of the microbe", resulting in antibiotic resistant mutations of bacteria. Fleming's prophetic warning is borne out more and more each year in clinical practice.

Starting in the 1950's, North America's livestock breeders have administered, as growth promoters, non-prescription antibiotics, in low doses to healthy animals – now predominantly in factory farms which raise thousands of livestock in confined spaces where bacterial infections spread freely.

In 2002, Dr. J. Conly, the Chairman of the Committee on Antibiotic Resistance in Canada reported in the Canadian Medical Association Journal (CMAJ) that ½ of all therapeutic antibiotics in the USA are prescribed by veterinarians (Ref.2). Considering the even greater quantities of antibiotics administered daily to healthy livestock in their feed, the usage of antibiotics in animals could be as much as 100 times that used for treating human diseases, as indicated by Dr. Khachatourians in the CMAJ in 1998 (Ref. 3).

In 2000, Canadian veterinarians were warned of antibiotic resistant C. difficile increasingly causing ulcerative bloody diarrhea in factory farms, "with piglets being most vulnerable" (Ref. 4). In 2001, the National Hog Farmer warned US producers that C. difficile " is sweeping the industry, killing many piglets" (Ref. 5). Thus, factory farms for antibiotic-fed pigs are major reservoirs of C. difficile superbugs. Increasingly, C. difficile that has particularly afflicted hospitals in Quebec, a Canadian province with large numbers of pig CAFO's.

Antibiotic resistant "superbugs" such as C. difficile may be transmitted to humans directly, from manure application to vegetable fields, or indirectly, via run-off to water sources, contaminating drinking water and swimming sites. The 2004 International Joint Commission (IJC) on Great Lakes Water Quality, commented that up to 40% of all gastrointestinal illness in the USA is waterborne. The IJC linked "the massive and largely unregulated use of antibiotics in agriculture" to "the increasing number of antibiotic resistant pathogens found in nature" (Ref.6). "In 1997, the WHO recommended that antimicrobials normally prescribed for humans be prohibited as growth promoters in animals" (Ref. 7).

One must realize, however, that fodder antibiotics create superbug mutations that are not only more robust and antibiotic resistant, but some acquire the ability to produce lethal toxins.

This scenario will continue even if classes of antibiotics are not for destined for use in humans.

Necrotizing entercolitis by Clostridium bacteria

Antibiotic resistant C. difficile is recognized as the cause of the deadly ulcerative enterocolitis known as pseudomembranous colitis and is appearing more frequently in North America. C. difficile infections occur most commonly in hospital patients whose protective colonic bacterial flora has been killed off by antibiotics prescribed for other conditions, allowing antibiotic resistant bacteria to flourish.

When broad-spectrum antibiotics are added to animal feed, the bacteria remaining alive in the manure must be resistant to the antibiotic used. The most easily killed bacteria are replaced by the surviving and reproducing variants that are not only antibiotic resistant, but are more robust and virulent (capable of causing human infections).

In the 1940s, before the widespread use of broad spectrum antibiotics in factory farms began in the 1960s, C. difficile (Clostridium difficile) was virtually unknown as a cause of disease, although other Clostridium organisms were well known as causes of necrosis of human tissues (such as the dreaded gas gangrene seen in war wounds prior to the antibiotic era) – and the production of deadly neuro-toxins (such as botulinum toxin of C. botulinum – and tetanus toxin of C. tetani).

With the routine addition of broad-spectrum antibiotics to the feed of factory farms, C. difficile has acquired the ability to produce necrotizing toxins (similar to gas gangrene Clostridia toxins), causing ulcerative, haemorrhagic bowel infections. As well, some C. difficile antibiotic-induced mutations are now producing potent neurotoxins, somewhat similar to the neurotoxins of C. botulinum (botulism toxin) and C. tetani (the tetanus toxin). These new aggressive, antibiotic-resistant, toxin-producing mutations are deadly – lethal particularly to the old, the young, the frail and those whose immune system is impaired by disease (e.g. - AIDs), or by chemotherapy.

A prime example of mutation into superbugs is E. coli 0157:H7, which evolved from a relatively benign colonic bacterium to become both destructively invasive and a toxin producer, resulting in haemorrhagic ulcerative enterocolitis (both in factory farm animals – and in human patients), with severe illness and deaths. These infections are complicated by intravascular coagulopathy (increased strokes and heart attacks from clotting) and, simultaneously, with a bleeding tendency and a risk of severe kidney damage. A significant factor in the increased danger is that the bacteria not only had become antibiotic resistant, but the mutated E. coli acquired the ability to produce the Shiga toxin – a powerful toxin produced by the Shigella flexneri bacteria, distant relative of E. coli (ref. 8).

These new toxic effects were revealed in Ontario's Walkerton E.coli 0157:H7 epidemic (2000) – an epidemic traced to municipal water contaminated from manure runoff from a regional livestock farm. Antibiotic-induced mutation created an E. coli strain, not only more robust and difficult to kill, but with the additional scourge of the potent Shiga toxin. We gave this deadly mutant strain a new designation, O157:H7

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This type of mutation to produce toxins would occur even if the fodder antibiotic were in a class of antibiotics not meant for use on humans!

Many thousands of deaths occurred in World War I from flesh eating wound infections (gas gangrene), caused by other members of the Clostridium family

(including C. perfringens and C. septicum). C. perfringens now is recognized as the third commonest cause of human ulcerative toxin-producing enterocolitis (Ref. 9) that is rarely fatal – unless it is the uncommon type C strain, with a high mortality (Ref. 10). Pertinently, C. perfringens necrotizing enterocolitis accounted for 4.9% of deaths in suckling pigs in factory farms, with antibiotic "acquired resistance in the course of time" cited as a factor. Swine were cited as the major animal carriers in the uncommon hyper virulent type C strain of C. perfringens (Ref. 11).

A particularly deadly form of Clostridium septicum infection, causes ulcerative enterocolitis in patients with impaired immune systems with low white blood cell counts, commonly associated with malignant disease (Ref. 12). A UK series, in patients with normal white blood cell counts suggested an increased risk of C. septicum super-infection in patients with E. coli 0157 infections and the hemolytic uremic syndrome (similar to the epidemic in Walkerton, Ontario, in 2000), noting a link between both of these bacteria and domestic livestock carriers (Ref. 13).

Neurotoxic effects of other Clostridia enterocolitis diseases

Although invasive AR Clostridium tetani enterocolitis has not been reported in humans, or animals, the occurrence of tetany and its extreme form, opisthotonus (the hallmark of human tetanus) have been described in calves, lambs and goats (Ref.10) and attributed to C. perfringens type C; this syndrome is sometimes so rapidly fatal that the underlying ulcerative enterocolitis isn't apparent.

Because often it has been difficult to implicate Clostridia infection definitely in rapidly fatal animal cases, these clinical signs suggest that enterocolitis from invasive C. tetani coexisted with C. perfringens because of tetanus- like clinical signs. A similar scenario is possible in humans, with antibiotic-induced mutations resulting in an invasive form of C. tetani enterocolitis. Tests should be developed and used to detect tetanus toxin in these cases because these bacteria are so difficult to grow for identification in the laboratory.

Clostridia grow in the same environments and thus may be exposed to the same stresses, (including exposure to antibiotics); it should be expected that different species of Clostridia could coexist as parts of a disease process. One of three successfully treated cases of infant botulism reported in 2005 had coexisting C. botulinum and C. difficile in the bloody diarrhoea (Ref. 14), with another similar case being cited (Ref. 15). Furthermore, botulism has surfaced in adults after the administration of antibiotics for C. difficile enterocolitis (Ref. 16). Botulism is generally the result of ingestion of food containing botulinum toxin produced by C. botulinum overgrowth.

Neonatal deaths from invasive Clostridium botulinum enterocolitis have been described increasingly since 1978, when it was suggested as an unrecognized cause of the sudden infant death (SID) syndrome (Ref. 17). Over 1200 cases of infant botulism were reported in the USA from 1976 to 1994, (Ref. 18). In Germany, 75 cases of unexpected sudden death in infants up to 12 months of age (including 57

classified as SID syndrome), showed free botulinum toxin in 9 and C. botulinum bacteria in another 6 (Ref.19), re-enforcing a link between botulism and SID syndrome. Neonates are not protected by the barrier effect of the normal colonic bacterial flora of adults. This allows C. botulinum to become invasive, producing toxic colitis.

Thus, in infants, Clostridial enterocolitis can produce flaccid paralysis through the botulism toxin, while there is the potential for a similar C. tetani enterocolitis producing the tetanic paralysis of tetanus infection. The toxins of botulism and tetanus are so lethal that death can occur before the underlying ulcerative enterocolitis becomes apparent in humans (as in children with SID), or animals (Ref. 10).

As an example of how difficult it is to grow Clostridia in culture, it was years before C. difficile was defined as the cause of antibiotic-induced deadly pseudo-membranous colitis; even now timely diagnosis is based on laboratory tests for its signature toxins. Thus, similarly, one may be able to identify botulism toxin in infants with early symptoms of muscle weakness or tetanus toxin in infants with increased muscle tone, before they become part of SID from C. bolulinum or C. tetani toxic enterocolitis.

Bacterial neurotoxins linked to autism and senile dementia (added 18/03/12) Unimaginable to Alexander Fleming, totally different species of bacteria [e.g. E. coli, C. difficile and methicillin resistant Staph aureus (MRSA)] in factory farm reservoirs can permanently share their antibiotic resistance genetic codes by "gene jumping" when they coexist is the same environments. This blending of genetic codes occurs between totally different disease organisms – in manure piles, in contaminated water and in the throats and colons of patients and staff on infectious disease wards – creating bacterial superbugs, some of which can thus become resistant to all antibiotics.

Also, the rise in the incidence of autism in children coincides with the rise in the incidence of antibiotic resistant Clostridia, like C. difficile (ref, 21). C. difficile disease is rapidly diagnosed now only because of the immunological identification of its toxins; if the toxins are present, so also is C. difficile. Some strains of C. difficile superbugs have now developed the ability to produce potent neurotoxins. Under the mutagenic influence of fodder antibiotics, some C. difficile strains, which produce potent neurotoxins, can become integrated into the bacteria that colonize the colons of children.

Even in very low concentrations, neurotoxins from C. difficile, C. botulinum and C. tetani may be damaging brain cells, or nerve pathways. Just as with any toxins, some patients suffer damage, or death, at much lower doses than others, probably on a genetic basis. If this were not so, there could not be an LD 50 dose to measure a toxin's lethality (50% of mice die – but 50% don't die). There must also

be a much lower dose, with which one percent dies and 99 percent live (an LD 1 dose). The LD factor only relates to patient death, but does not consider neurologic damage that doesn't cause death. Thus, some patients can suffer damage to brain cells and nerve pathways at very low concentrations. Colonization of children's colons by any (or several) of the potent neurotoxin-producing enterocolitis Clostridium pathogens (difficile, botulinum, tetani, histolyticum and sordellii) – even without clinical signs of bowel infection – has the potential to damage brain cells, or their synapses or pathways – by continuing to release relatively small concentrations of neurotoxins.

The rise in the incidence of autism has paralleled the rise in the incidence of antibiotic resistant C. difficile enterocolitis; C. botulinum and C. tetani are similarly intestinal bacteria and have been identified as being involved in human enterocolitis infections.

C. botulinum enterocolitis has been linked to sudden infant death syndrome (SID) for many years (ref, 22). Autism patients have a high incidence of gastrointestinal problems, including bowel infections – and they often have a history of multiple courses of antibiotic therapy. Antibiotic therapy has significant influence on the makeup of the bacterial flora in the colon. Broad-spectrum antibiotic treatment (vancomycin), aimed at eliminating C. difficile, has a positive clinical effect in some cases of autism in children.

Another perplexing neurologic problem that is similarly rising in incidence is Alzheimer's disease. Could some of this increase be related to a chronic low level of bacterial neurotoxin poisoning from Clostridium superbugs making up part of the colonic bacterial flora? Additionally, if there is E. coli 0157:H7 colonization, the increase in clotting that may be induced by the 0157:H7 toxins, may predispose to many small strokes and progressive dementia.

Arresting and even allowing some regenerative healing of the central nervous system also may be possible if one replaces neurotoxin-producing bowel bacteria by encouraging colonic colonization with normal bowel bacteria. Because antibiotic treatment is fraught with many dangers (including proliferation of other virulent toxin producing superbugs) – the re-establishment of a normal colonic bacterial flora by enemas using stool emulsions from normal healthy donors makes common sense, is low risk, low-tech and low in cost. Even the use of low cost lactobacillus capsules (available over-the-counter in drug stores as "pro-bacteria) may suppress an overgrowth of Clostridia in the colon.

Recently, the destruction of the normal bacterial colonization of the colon by broad-spectrum antibiotics (vancomycin) has been linked to the increasing incidence of asthma in children. Normal colonic bacteria may stimulate the development of our immune responses. Killing off the normal bacterial flora may be interfering with this normal immunity-development process, fostering an asthma response that would not have occurred normally.

Sadly, in the USA, private medical treatment is so profit driven that low cost, effective treatments may be discouraged by the suppliers in favour of more profitable (expensive) methods that may be less effective; this philosophy may be most evident in the active suppression (by intentional low production at the manufacturing level) of low-cost (low-profit) generic drugs (like generic methotrexate which is an essential drug for treating childhood leukemia).

Skyrocketing health care costs in the USA are intertwined with doctor remuneration; doctors often have financial ties to the treatment facilities to which they refer their patients – the pharmacies, the hospitals, the x-ray departments, blood testing laboratories, the home nursing, the physiotherapy – fostering overuse of the most expensive treatments (including the most expensive antibiotics) (Ref . 23).

The pharmaceutical industry continues to profit from the use of massive amounts of antibiotics in factory farm fodder, resulting in toxin-producing, antibiotic-resistant bacteria that spread from manure to water supplies and farm produce to patients who end up in hospital infectious disease wards. These superbug infections are then subjected to prolonged courses of treatment with combinations of newest and most expensive antibiotics – a very lucrative path for the pharmaceutical industry – on a trail littered with superbug infections and death.

We should have heeded Alexander Fleming's words of timeless wisdom in Stockholm as the antibiotic era dawned. In 1945, as he accepted the Nobel Prize for the discovery of penicillin, he warned against the use of sub-therapeutic doses of antibiotics "bought by anyone in the shops" without a prescription: "*The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to Resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death?"*

Conclusions

In the "massive" use (in healthy animals) (Ref. 6) of sub-therapeutic doses of antibiotics, bought "at the shops" (animal feed stores without prescription) (Ref.1), factory farms "have changed the nature of the microbe" (Ref.1), resulting in widespread manure reservoirs of virulent antibiotic resistant superbugs. C. difficile has mutated into lethal, invasive, toxin-producing, antibiotic resistant strains and – like the other pathogenic Clostridia – produce heat- and antiseptic-resistant spores, which can survive for many years. The rise of mutant, antibiotic-resistant superbugs – warned of by Fleming in his 1945 Nobel lecture, "Penicillin" – is now a reality.

In 2000 the World Health Organization warned that antibiotics should not be a substitute for "high quality animal hygiene". By applying this principle, European "farmers who stopped relying on antimicrobials as growth promoters in livestock , have experienced no economic repercussions" (Ref. 7).

Bacteria can decrease their acquired genetic antibiotic resistance in only a few years because bacteria go through as many generations in a few months that mankind has undergone since the rise of Homo sapiens. When antibiotics are no longer attacking bacteria, non-spore-forming bacteria soon begin to lose their antibiotic resistance.

Canada and the rest of North America has not followed Europe's lead in prohibiting the abuse of antibiotics in livestock operations.

With timeless wisdom, Cicero, at the senate, voiced imperatively: "Salus populi suprema lex esto!" ("The health of the people reigns supreme!") (Ref. 20) .

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