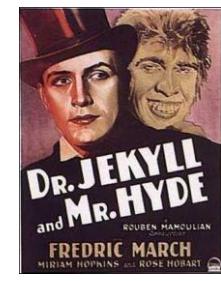


Clostridium botulinum the Dr. Jekyll and Mr. Hyde bacteria



INTRODUCTION

Clostridium botulinum is a Gram-positive, rod-shaped bacterium that produces the most potent substance known → the botulinum toxin (BoNT), responsible of the neuroparalytic illness called botulism.

1ug is lethal to a person and only 1g of crystallized toxin is enough to kill a million people!!
C. botulinum can produce 7 different types of neurotoxin, distinguished by their antigenic characteristics.

It is an obligate anaerobe with peritrichous flagella and oval subterminal spores.

This microorganism was first recognized and isolated in 1895 by Emile van Ermengem who described the toxicological mechanisms of action responsible for botulism.

This organism and its spores are globally distributed in nature (both terrestrial and aquatic ecosystems) but it's particularly interesting because it can grow in almost any type of food

As Dr. Jekyll and his alter ego, Mr. Hyde, BoNTs also possess two seemingly disparate characteristics: is a widely utilized therapeutic and cosmetic agent, and the cause of the lethal botulism.

The objective of this work is to familiarize the ordinary people with *C. botulinum* and this two sides

Mireia Claver Aragón
Microbiology degree

Universitat Autònoma de Barcelona 2013

Comparing the 16s rRNA sequences of the strains of *C. botulinum*...

Group Features	GROUP I	GROUP II	GROUP III	GROUP IV
Toxin types	A, B, F	B, E, F	C, D	G
Proteolysis	+	-	Weak	+
Disease host	Humans	Humans*	Birds and mammals	Humans**
Toxin gene	Chromosome	B and F in chromosome; E on bacteriophage	Bacteriophage	Plasmid
Habitat	Terrestrial/aquatic	Terrestrial/aquatic	Aquatic	Terrestrial

*Toxin E causes botulism almost exclusively in aquatic animals.

** It has been associated to sudden death but not with the neuroparalytic disease

THERAPEUTIC USE

BoNTs are now the most widely used therapeutic proteins → Due to their high efficacy, tolerance, longevity and satisfactory safety profile

TABLE 2. BoNT Preparations	
BoNT-A	BoNT-B
• Botox Cosmetic®, Vistabel®, Vistabex® (US)	• Myobloc® (US)
• Dysport®, Reloxin® (Europe)	• Neurobloc® (US)
• CBTX-A, Prosigne® (China, selected Asian and South American countries)	
• Neuronox® (Korea, North Africa, Eastern Europe, Russia, and Mexico)	
• Xeomin® (Germany)	

Lu DW, Lippitz J. Complications of botulinum neurotoxin. *Dis Mon.* 2009.

Current indications approved by US FDA

Strabismus, Blepharospasm, Hemifacial spasm, Cervical dystonia, Glabellar facial lines, Axillary hyperhidrosis, Chronic migraine, Neurogenic detrusor overactivity, Upper limb spasticity, Overactive bladder, Urinary incontinence, Cosmetic use

Botox (BoNT/A)

Botox is the most common non-surgical cosmetic procedure worldwide

- Such use has increased by 4700% since 1997
- The effects last about three to four months

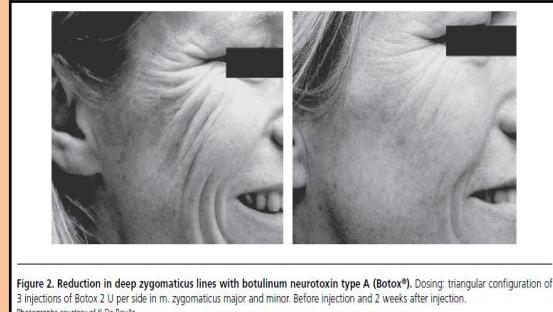


Figure 2. Reduction in deep zygomatic lines with botulinum neurotoxin type A (Botox®). Dosing: triangular configuration of 3 injections of Botox 2 U per side in m. zygomaticus major and minor. Before injection and 2 weeks after injection. Photographs courtesy of K. De Boule.

De Boule KL. Botulinum neurotoxin type A in facial aesthetics. *Expert Opin Pharmacother.* 2007

CONCLUSIONS

- Although *Clostridium botulinum* is a microorganism that has been studied much, there is still much research to be done!
 - All aspects involved in its mechanism of action, how can we prevent and/or stop the intoxication as soon as possible to avoid the disease...
- Even though botulism is not very frequent nowadays, we have to keep it in mind due to its high mortality and its possible use in a large-scale terrorist attack.
- The future of BoNTs in therapeutic applications is bright, yet more research is needed to improve their medical uses.
 - Study the mechanism of action in every application, approve more indications by the FDA and discover new ones

BoNTs block the release of acetylcholine attaching to the end of the motor neurons in the neuromuscular junction, which does not allow the interaction between this neurotransmitter and the muscle receptor, preventing the nerve impulse from reaching the muscle, and the muscle contraction cannot be produced

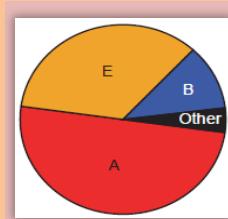


Figure: Serotypes that produce food-borne

Davletov B, Bajohrs M, Binz T. Beyond BOTOX: Advantages and limitations of individual botulinum neurotoxins. 2005

BOTULISM

- Types of botulism
 - Food-borne botulism: ingestion of food containing preformed BoNT (mainly home-canned foods)
 - Infant botulism: consuming the spores, which then germinate in the intestines and release the toxin *in vivo*
 - Wound botulism: organisms multiply and produce toxin in a contaminated wound
 - Hidden botulism or Adult Intestinal Colonization Botulism: no apparent source of botulinum toxin found
 - Inadvertent or iatrogenic botulism: accidental occupational exposure or complication in their therapeutically use
 - Inhalational (bioterrorism)

■ Symptoms: A characteristic acute, symmetric, descending flaccid paralysis with prominent bulbar palsies

■ And visual disturbances, dry mouth, difficulty swallowing...

■ Mortality: In the past 50 years has fallen from about 50% to 3-5%

■ Diagnosis: The standard confirmatory test for botulism is a Mouse Bioassay → presence of the neurotoxin in a food sample, patient's blood, gastric contents or stool

■ Therapy: Passive immunization with H-BAT antitoxin (against all 7 BoNT) or BabyBIG-IV (for infants) + supportive care + rehabilitation

□ Immunization: There is no routine vaccination against botulism and antitoxins are not useful for preventive purposes

■ Vaccine under development: Recombinant Botulinum Vaccine (rBV A/B)

Prevention



Category A select agent (CDC)

Botulism toxin as a biological weapon	
Advantages	Disadvantages
Most poisonous substance known	Constraints in concentrating and stabilizing the toxin
High lethality (1 aerosolized gram → kill 1 million people)	Rapid degradation in the environment (minutes)
Delivered by contaminated food, water or in an aerosol form*	Rapidly inactivated by standard water sanitation protocols
Cause public panic and social disruption	Does not penetrate into the skin (high weight)
Require special action for public health alertness	Not transmissible from person to person
Colorless, odorless and tasteless	

Botulism is likely to occur as SPORADIC ATTACKS, due to the difficulties in dispersing the toxin