Here, there, and everywhere

Dr. CH Ng, AC,

ICU KWH

20/01/2015

Case 1

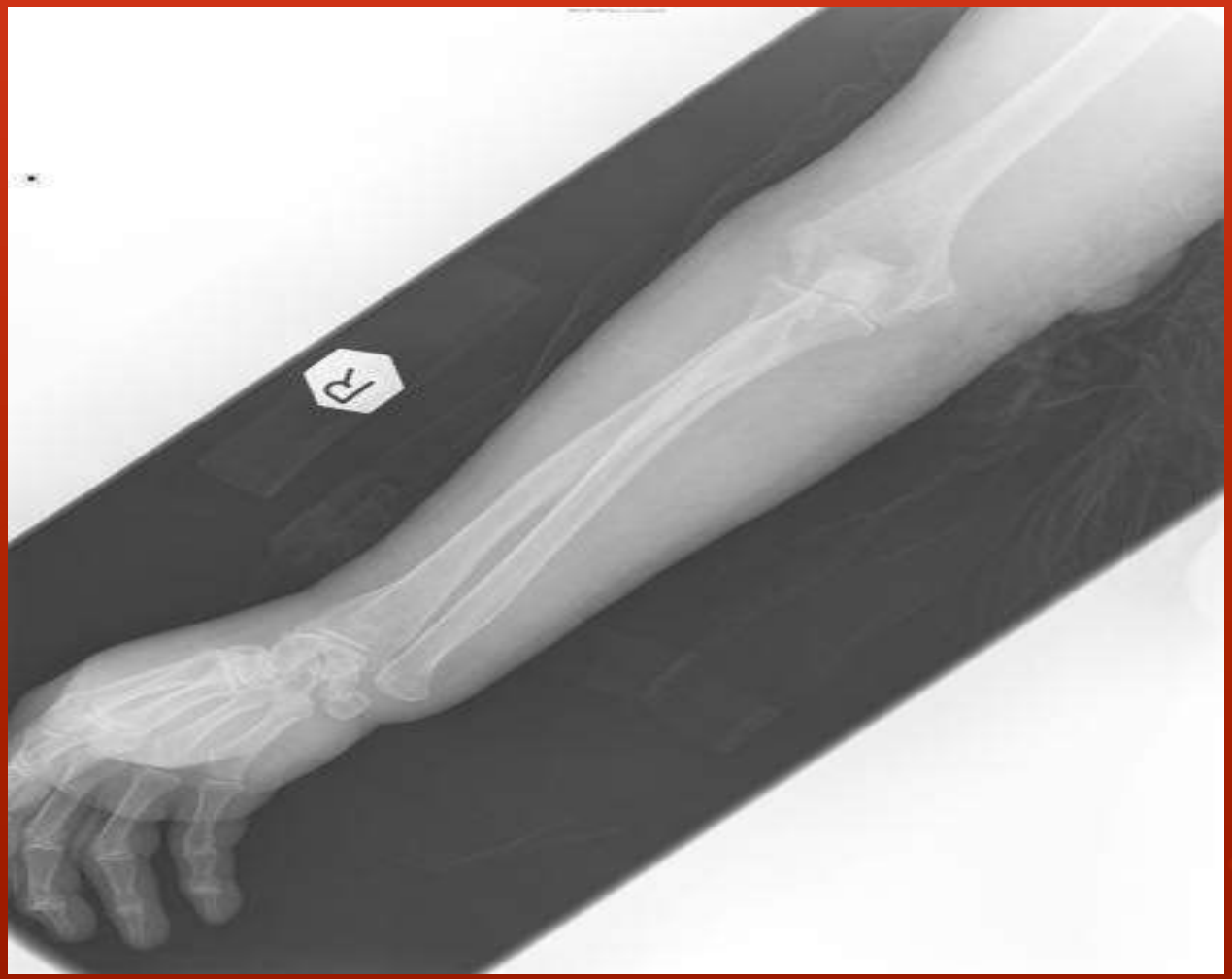
- 86/F
- HT, hyperlipidaemia, DM
- OA knees, spinal stenosis
- RTA with knee surgery
- ADL independent
- c/o Rt UL swelling since 14/01/2011
- Increasing pain with blisters
- Admitted into O&T ward on 15/01/2011 at 0129
- P/E: normal respiratory and cardiovascular systems; erythema over Rt UL with haemorrhagic blisters at medial aspect
- Stable haemodynamics

Case 1

- WCC 3.1
- Plt count 129
- Hb 11.1
- Cr 82 rose to 228

- CXR clear

XR Rt forearm



Case 1

- Emergency operation done
- OT findings: Rt arm necrotising fasciitis extending from the axilla to the wrist, mainly on the ulnar side
- Severe hypotension during operation
- Postop ICU care
- On Augmentin + Levofloxacin
- Double inotropic support
- ARF, DIC, CVVH started
- She passed away on the same date at 1715

Case 1

- Blood culture: no organisms
- Wound swab and tissue culture: Group G Streptococcus
- A case of NF caused by Group G Streptococcus

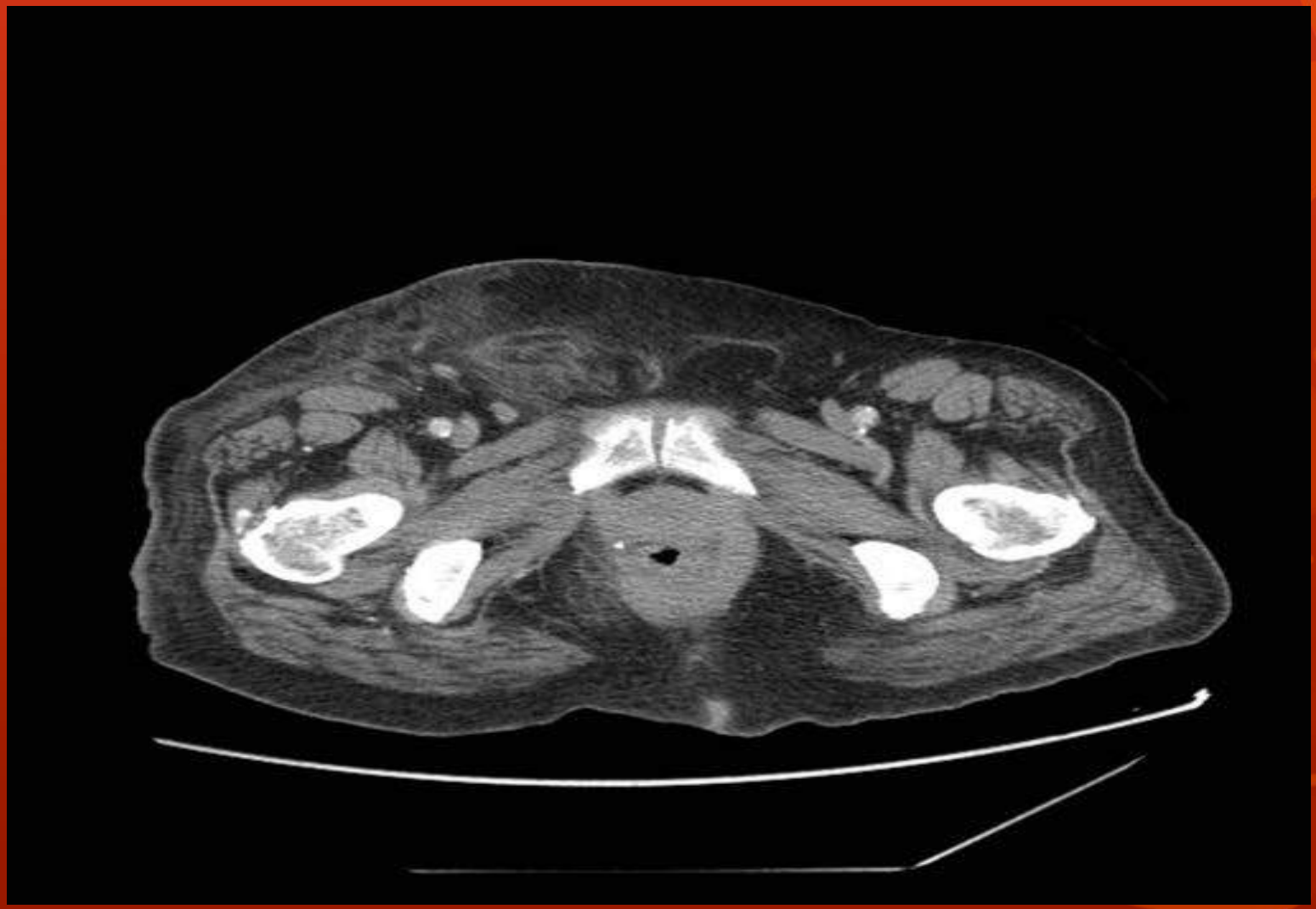
Case 2

- 49/F
- HT, hyperlipidaemia
- DM with retinopathy, ESRF on CAPD
- Hypothyroidism on T4 replacement
- Anaemia (no OGD/colonoscopy done before)
- c/o decreased GC with fever, admitted into Medical ward
- P/E: respiratory and cardiovascular systems normal; a swelling over Rt suprapubic area with overlying greyish skin

Case 2

- WCC 25 with neutrophil predominance
- Hb 8.4 (baseline 8-10)
- Plt count 223
- Ur/Cr 31.5/884
- A/G 20/38
- CXR clear
- Blood culture, MSU culture, and PDF culture: no organisms
- On Augmentin, and later added Levofloxacin

CT scan



Case 2

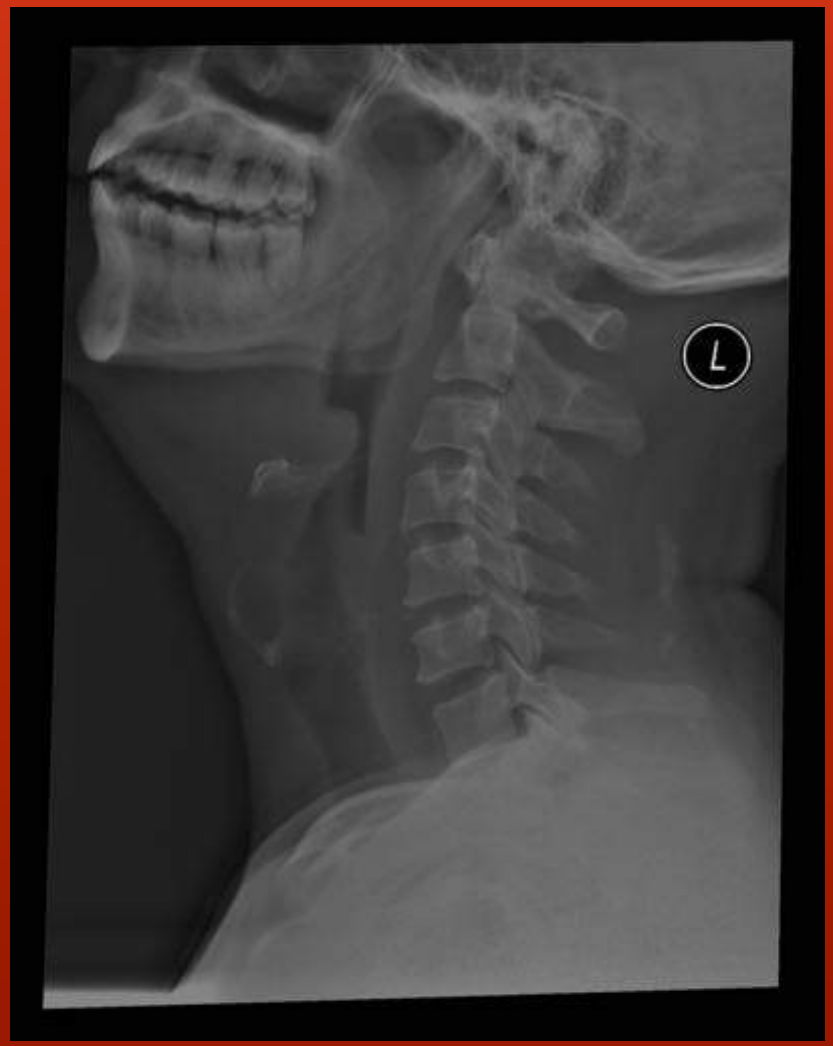
- Planned for I & D
- But OT findings: extensive necrotising fasciitis with pus involving Rt lower abdominal wall tracking down Rt groin, vulva, and ischial tuberosity, with rectum intact
- Tissue and pus culture: Lactobacilli
- Further Hx from patient: normal menses with no abnormal PV discharge

- A case of NF caused by Lactobacilli

Case 3

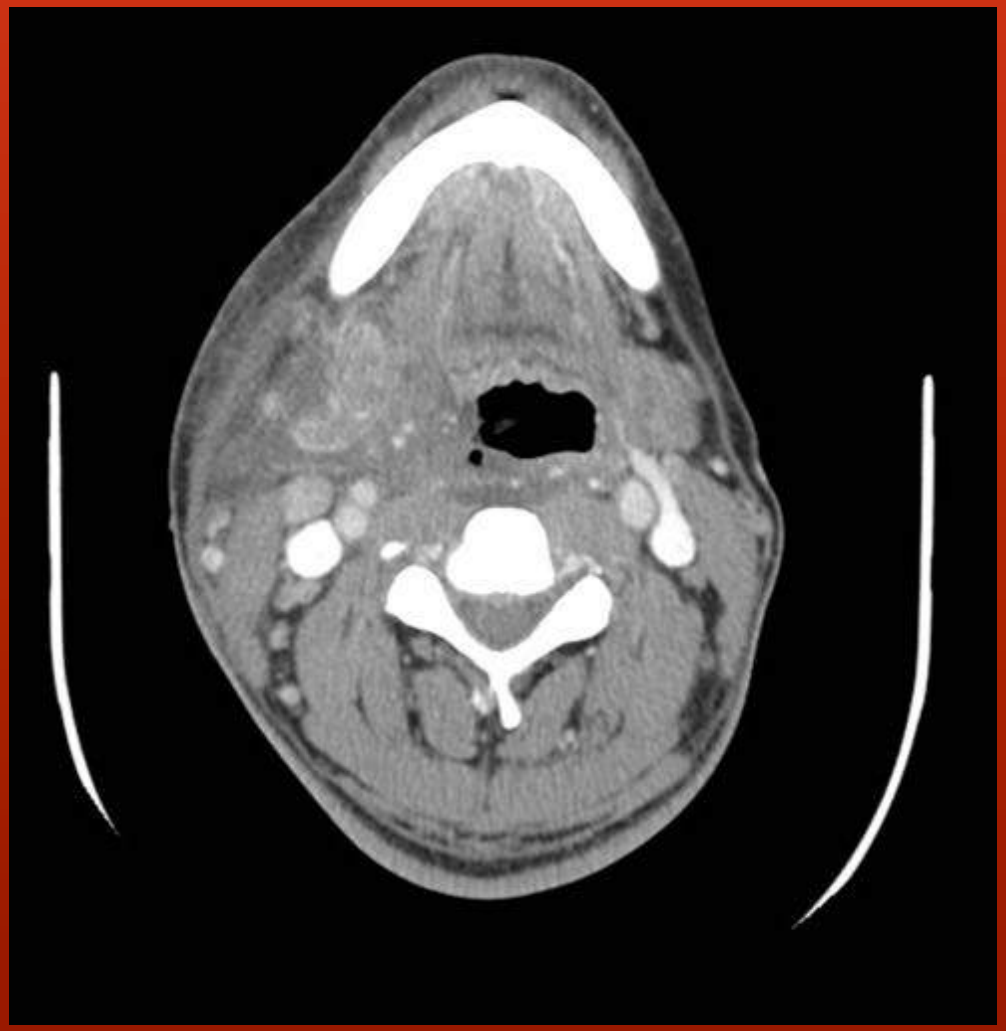
- M/55
- Smoker
- GPH
- c/o sore throat x few days, with dysphagia and fever
- Admitted into Surgical ward
- No SOB/stridor
- No drooling of saliva
- P/E: normal respiratory and cardiovascular systems; swollen and tender Rt tonsil
- CXR clear

XR neck

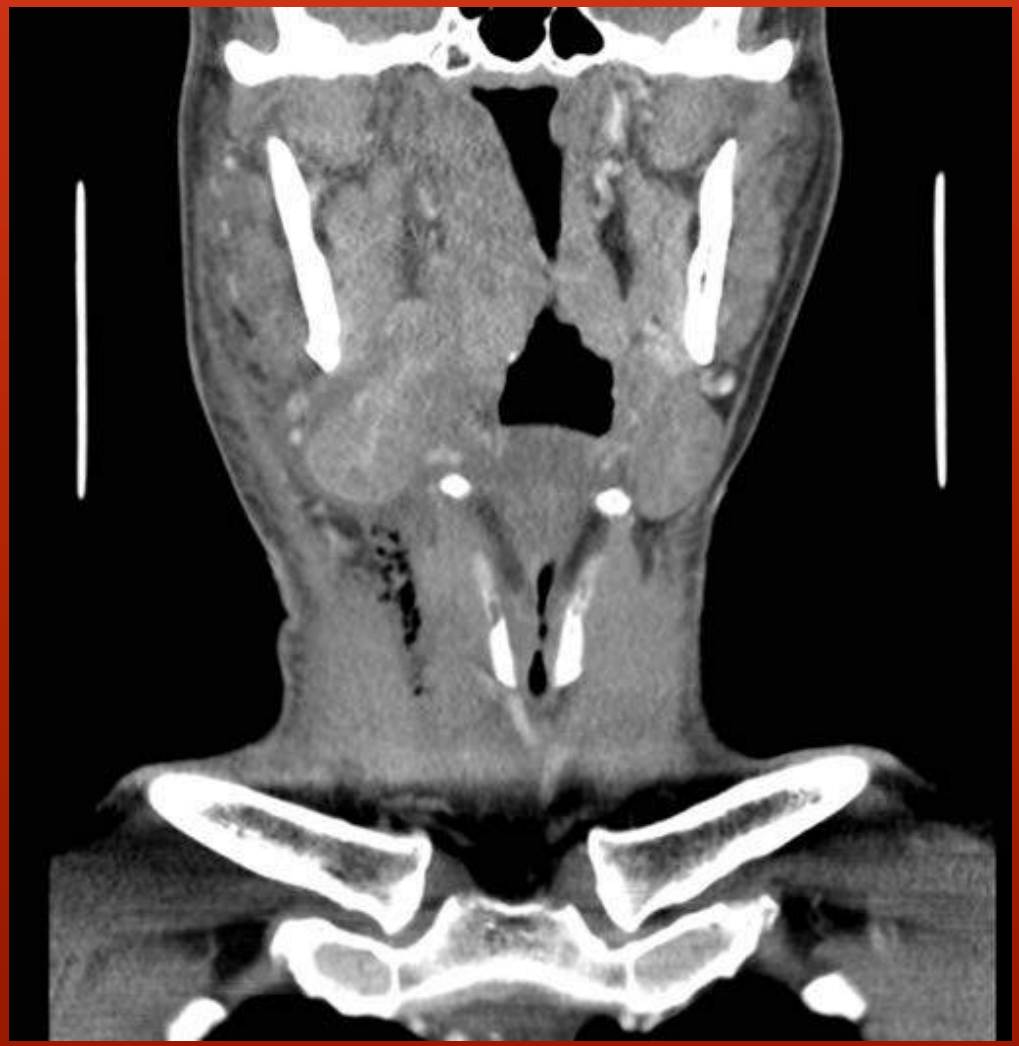


- WCC 13.6
- Normal Hb and Plt count
- INR 1.36
- Cr 107
- RG 7.1
- CRP 224

CT neck with contrast



CT neck with contrast

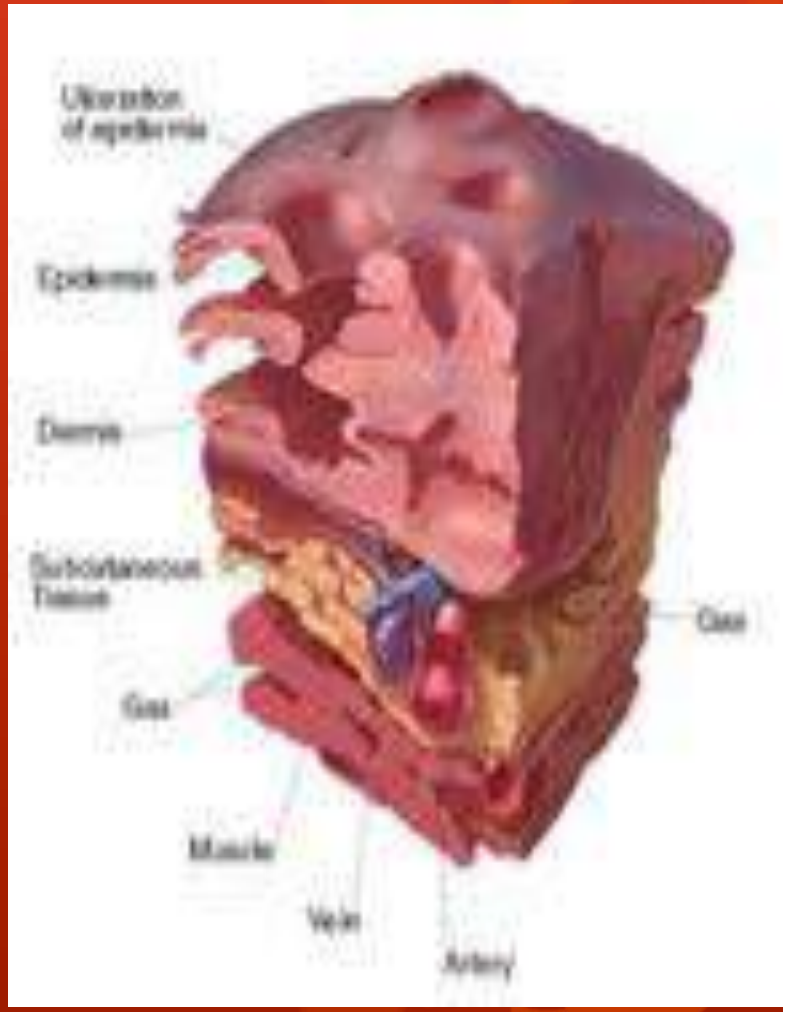


Case 3

- Emergency operation done on 24/10/2014
- OT findings: extensive abscess involving Rt peri-tonsillar, retro-pharyngeal, para-pharyngeal regions, and Rt neck along the SCM, and greyish, dusky fascia along the SCM, with smelly turbid fluid, and +ve finger test
- Repeated debridements and dressings done in OT and ICU
- Tissue cultures: Parvimonas micra, Prevotella intermedia, and Eggerthella lenta (anaerobes)
- On Augmentin, Flagyl, and Clindamycin
- Anti-HIV Ab-ve

- A case of NF caused by anaerobes

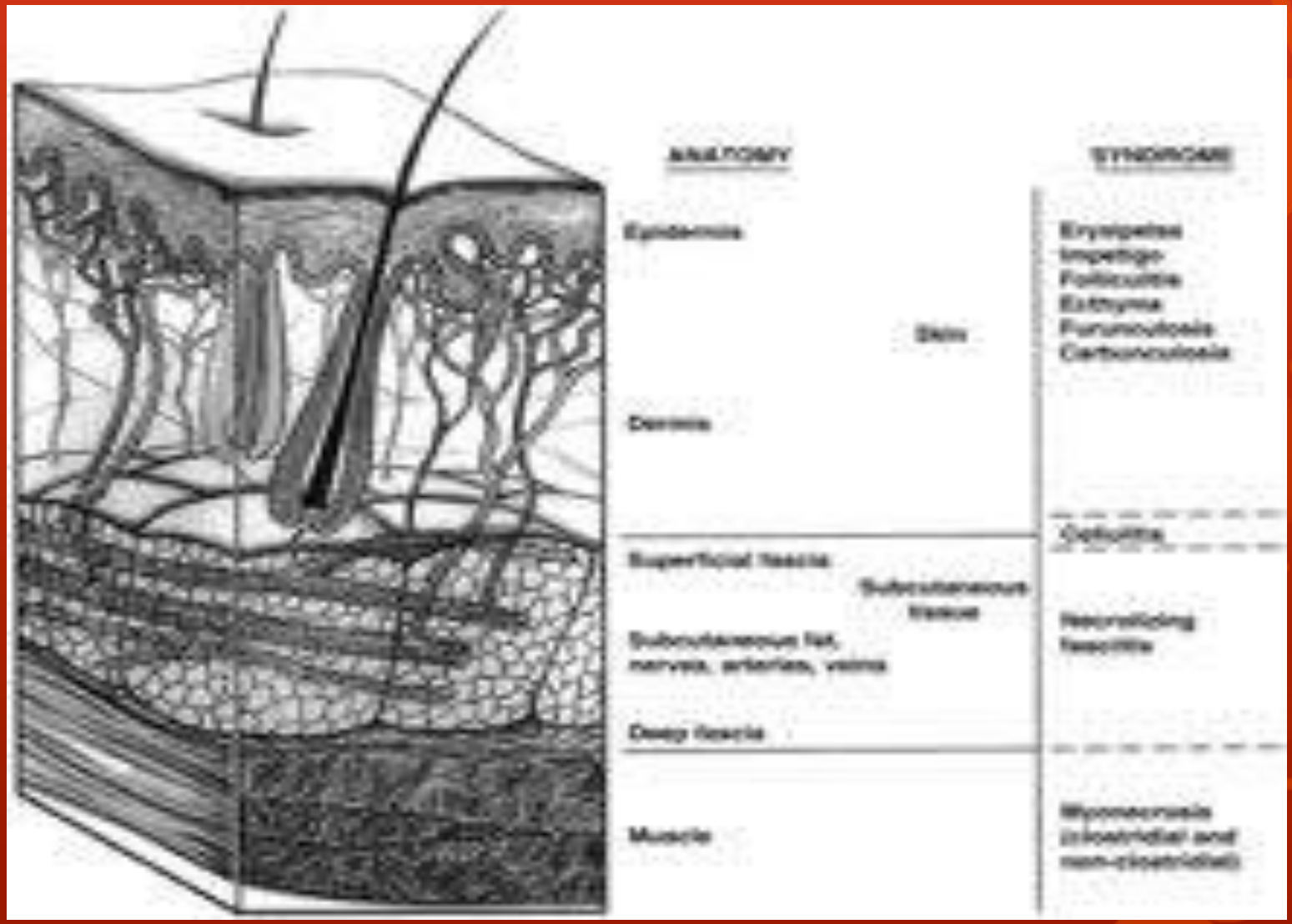
Necrotising Fasciitis
壊死性筋膜炎



Necrotising fasciitis

- A progressive, fulminant bacterial infection of subcutaneous tissue which spreads rapidly through the fascial planes causing extensive tissue destruction
- Can affect any part of the body
- A rare but potentially lethal condition
- Prompt recognition and intervention is essential as mortality is directly proportional to time to intervention

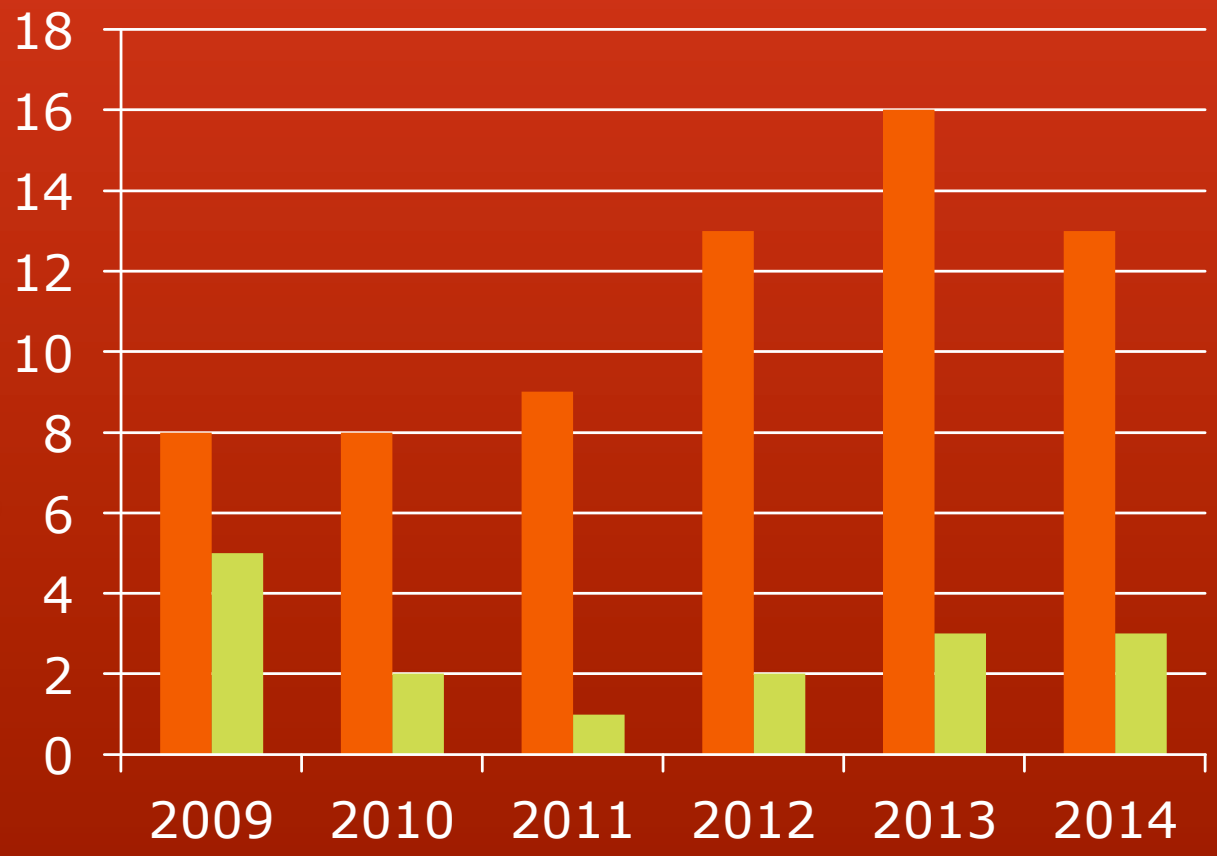
Necrotising fasciitis



Necrotising fasciitis

- The USA reports an annual age-adjusted incidence of 4.3 invasive infections per 100000 of the population
- In Australian studies, it is reported as a maximum yearly incidence of 3.8 cases per 100000
- Reported mortality in the literature varies widely with more recent studies reporting a mortality of ~ 25%

Situation in HK from CHP



M:F=46:21

37-89 (68.24)

Mortality rate=24%

GAS:5
Vibrio vulnificus:60
Others:2

History

- Hippocrates era:
  - As early as the 5th century BC, the writings of Hippocrates already described outbreaks of erysipelas affecting patients
  - His description of a massive amount of tissue destruction depicts the classical picture of GAS (Group A Streptococcus) necrotising fasciitis:

  - **'The erysipelas would quickly spread widely in all directions. Flesh, sinews and bones fell away in large quantities…Fever was sometimes present and sometimes absent…There were many deaths. The course of the disease was the same to whatever part of the body it spread.'**
  - Before the antibiotic use, NF was treated successfully with 'bear-claw scratch debridement' and tubes irrigating the tissues with Dakin's solution of chlorinated sofa

History

- 18th – 19th century:
  - In 1924, a Beijing missionary surgeon reported similar conditions among the opium addicts
  - From the 18th and 19th century the British naval surgeons referred to NF as 'hospital gangrene'
  - The first modern report that describes a detailed case of 'hospital gangrene' was reported by Joseph Jones, a Confederate Army Surgeon during the American Civil War
- Over the years, many terms have been developed and used such as flesh-eating bacteria syndrome, suppurative fasciitis, and streptococcal gangrene

History

- ‘Meleney’s gangrene’ is commonly used for abdominal fasciitis, but strictly speaking should be streptococcal dermal gangrene on any part of body
- ‘Fournier’s gangrene’ represents NF of the perineum, caused by either GAS or other organisms
- The term NF was coined by Wilson in 1952, to delineate the histological appearance of the disease, that is, an invasive necrotising infection involving deep fascia and soft tissue

Classification

- Anatomical location:
  - Cervical
  - Thoracic
  - Abdominal (Meleney's)
  - Pelvic
  - Fournier's gangrene
  - Limbs

Classificaton

- Microbial cause:
  - Type I
  - Type II
  - Type III
  - Type IV

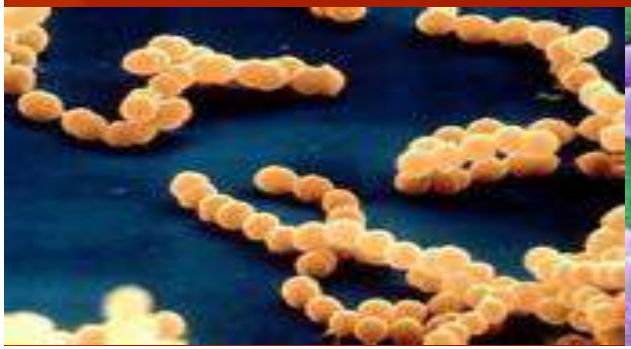
Classification

- Type I NF (polymicrobial/synergistic):
  - Consists of 80% of NF
  - Caused by a combination of anaerobic, aerobic, and facultative anaerobic bacteria
  - Commonly affects the immunocompromised



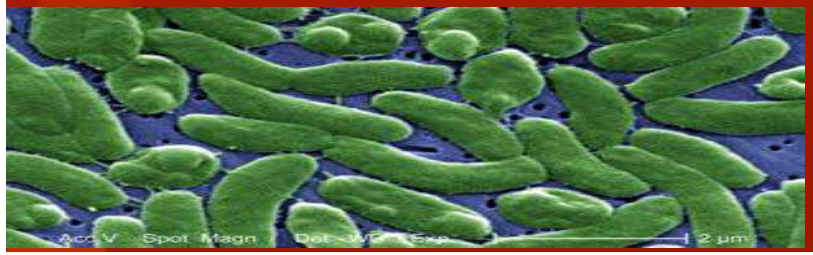
Classification

- Type II NF:
  - Around 20% of NF is caused by a single organism
  - Commonly from Gram +ve organisms
  - Frequently caused by either GAS or Staphylococcus aureus
  - Recently saw an increase in the epidemic strains of MRSA causing NF in USA, associated with purpura fulminant of Meningococcal septicaemia



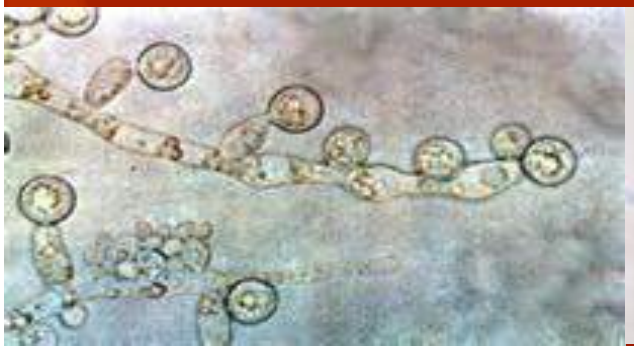
Classificaiton

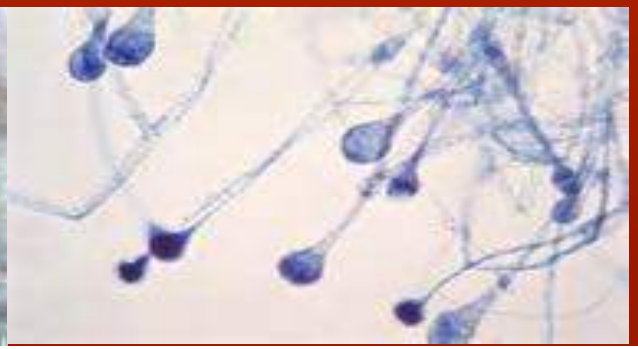
- Type III NF (Gram –ve monomicrobial, including marine-related organisms):
  - The commonest remains the Vibrio species, for example, V. damselae and V. vulnificus that were responsible for cases of NF in HK in 1990s
  - Affects patients with liver disease and haemochromatosis
  - Wound contamination with seawater accounts for ¼ of cases
  - Other Gram-ve monomicrobial NF is uncommon but may be caused by Pasteurella multocida, H. influenzae, Klebsiella species, and Aeromonas species



Classification

- Type IV NF (Fungal):
  - Usually affect immunocompromised patients
  - Can be Candida or Mucor and Rhizopus species
  - Zygomycotic NF may occur after trauma and are responsible for almost 1/3 of NF cases





Causative organisms

Organism	No. of cases
Streptococcus species[a]	31
Staphylococcus aureus	26
Klebsiella species	17
Enterococci	14
Acinetobacter baumanii	13
Escherica coli	12
Pseudomonas aeruginosa	10
Enterobacter species	6
Proteus species	6
Bacteroides species	6
Fungi (*Candida* species)	5
Peptostreptococcus species	4
Clostridium species	2
Other[b]	10

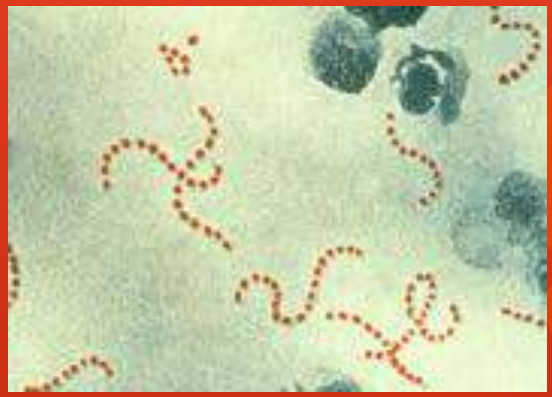
NOTE. Data are adapted from [16].

[a] *Streptococcus pyogenes* (14 cases), group B *Streptococcus* (13), group G *Streptococcus* (3), and *Streptococcus milleri* (1).

[b] Includes *Chryseobacterium* species (1 case), *Meningosepticum* species (1), *Propionibacterium* species (2), *Morganella morganii* (1), *Veillonella* species (1), *Bacillus* species (1), *Aeromonas* species (1), *Burkholderia pseudomallei* (1), and *Vibrio vulnificus* (1).

Microbiology

Microbiology



- **Group A Streptococcus (GAS)** 化膿性鏈球菌:
  - Streptococcus pyogenes is a spherical Gram+ve bacterium which displays streptococcal group A antigen on its cell wall
  - Incubation period 1 – 3 days
  - An infrequent but usually pathogenic part of the skin flora

Pathophysiology

- For decades, previous hypotheses believed that the extracellular proteases and other secreted GAS molecules are the main contributors to the invasive process of NF
- But, with development of new molecular biology techniques, it is now believed that the pathogenesis of NF consists of complex interactions between the pathogen and the host

Pathophysiology

- **GAS**
  - GAS secretes a large number of virulence factors that contribute to the molecular pathogenesis of NF
  - Importantly, many complex and overlapping pathways exist and some of the GAS proteins have multiple functions
  - A subset of virulence factors , for instance, **SpeB** and **Ska/ Plasmin** directly damage the host tissues, degrade the extracellular matrix proteins, and induce vascular dissemination via their enzymatic pathway

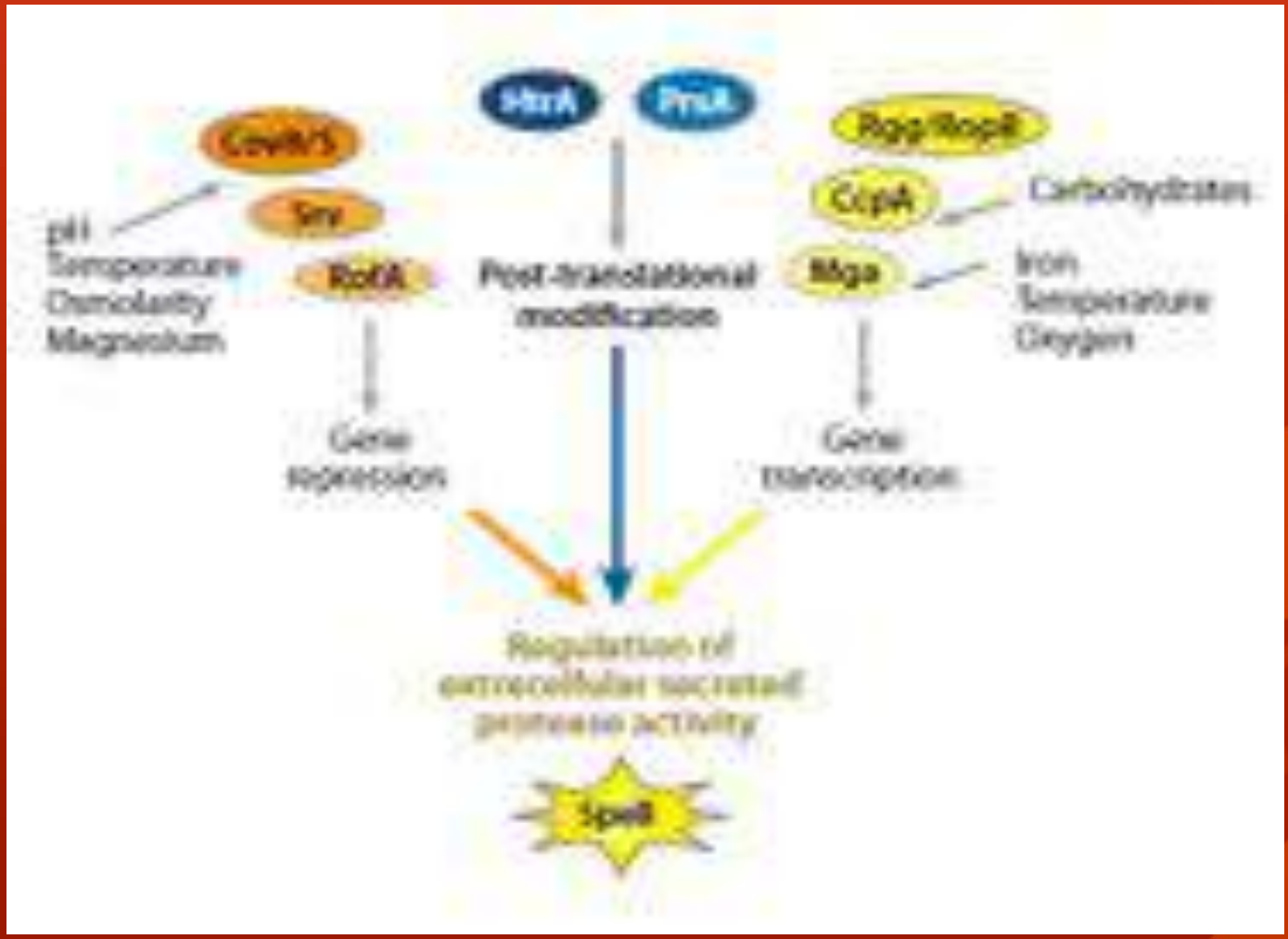
Pathophysiology

- Other virulence factors such as **SpyCEP** and **Mac1/IdeS** indirectly damage the host tissue by cleaving immune molecules, inactivate PMN and stimulate release of pro-apoptotic molecules
- Host matrix metalloproteinases (**MMPs**) and coagulopathy are also implicated in GAS NF

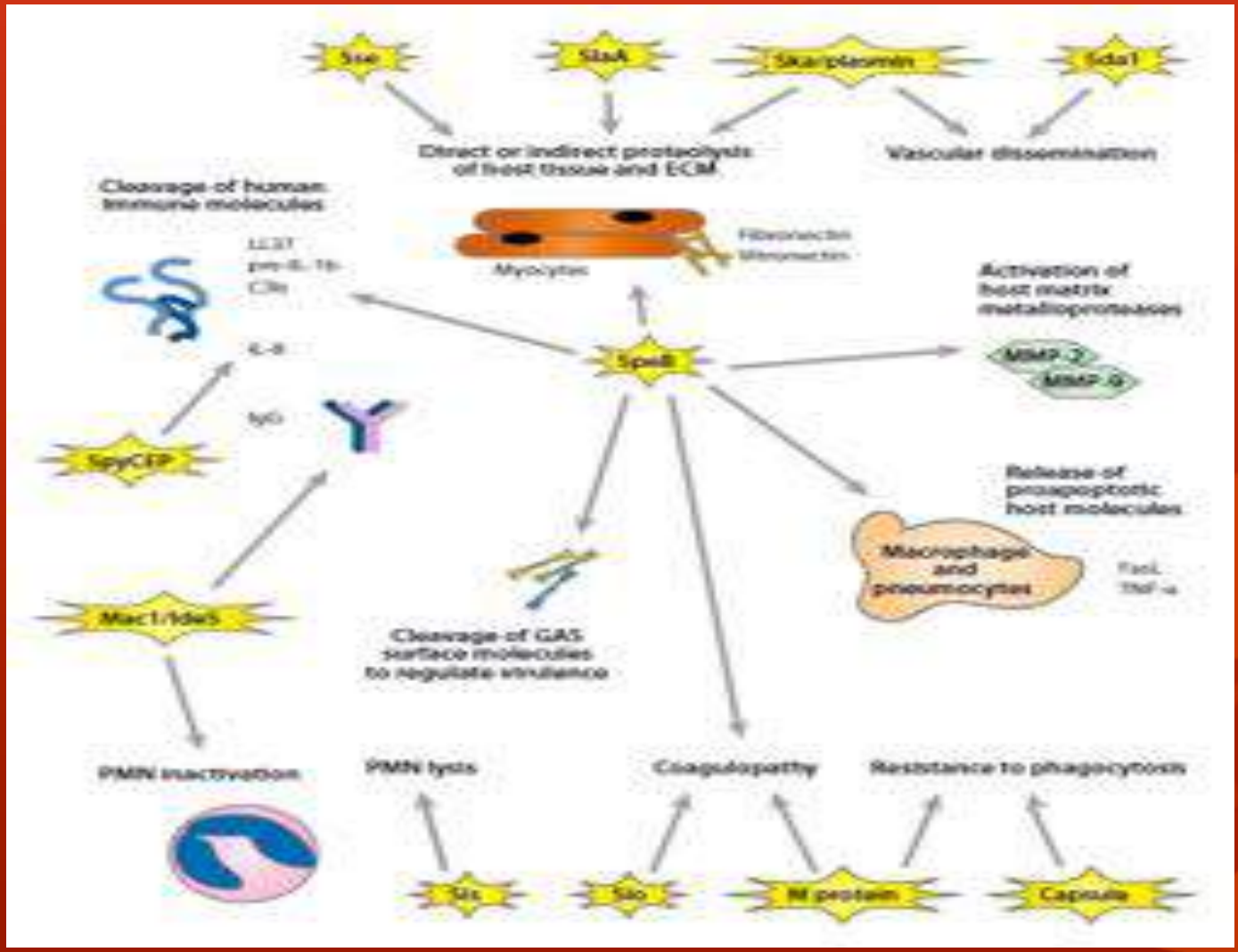
Pathophysiology

- GAS organisms undergo a very complex molecular transition during the progression from a localised to an invasive infection
- **SpeB**, a broad-spectrum cysteine protease virulence factor, is regulated by multiple intersecting and collateral pathways that respond to different environmental stimuli
- **SpeB** is repressed, activated and regulated by multiple regulatory pathways
- The combined effects result in an in vivo temporal-spatial expression pattern of **SpeB**

Pathophyiology



Pathophysiology



Pathophysiology

- **Exotoxin**
  - Production of various exotoxins can enhance the virulence and accelerate progression of infection
  - Staphylococcus aureus and Streptococci elaborate surface proteins M-1 and M-3, exotoxins A, B, and C, streptolysin O, and superantigen
  - The M proteins increase the microbes' ability to adhere to tissue and escape phagocytosis
  - Toxins A and B, damage endothelium, cause loss of microvascular integrity, and escape of plasma, that results in tissue oedema and impaired blood flow

Pathophyiology

- In addition, these toxins, together with streptolysin O, stimulate CD4 cells and macrophages to produce large amounts of TNF, IL-1 and IL-6
- Systemic release of cytokines produces the systemic inflammatory response which progresses to septic shock, multi-organ failure and death
- TNF also induces additional injury to the vascular endothelium by stimulating neutrophil degranulation
- As a result, the complement system and coagulation cascade is activated, worsening small vessel thrombosis and tissue ischaemia
- The tissue ischaemia impedes the oxidative destruction of bacteria by PMNs and prevents adequate delivery of antibioitcs
- Thus, surgical debridement is the mainstay treatment of NF and antibiotics alone are not useful

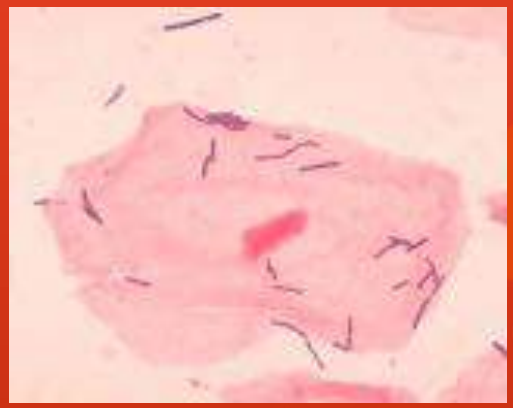
Microbiology

- **Vibrio vulnificus** 創傷弧菌:
  - Gram-ve, motile, curved, rod-shaped bacterium
  - Present in marine environments such as coastal areas
  - First isolated in 1976
  - Incubation period 12hrs – 72 hrs

Pathophysiology

- Few cytotoxins involved:
  - VvRtxA: key toxin which triggers excessive production of reactive oxygen species ➔ cytotoxicity
  - Haemolysin (VvhA): exotoxin; causes cell death by pore formation in the cellular membrane
  - VvpE: extracellular metalloprotease; its purified form causes tissue necrosis and bullous lesions, degrades type IV collagen (structural component in basement membrane), also activates procaspase 3, a protein in cellular apoptosis

Microbiology



- **Lactobacilli** 乳酸菌:
  - Gram+ve facultative anaerobic or microaerophilic rod-shaped bacteria
  - Converts lactulose and other sugars to lactic acid
  - In human, present in vagina and GIT, and are benign
  - Some species are used in production of cheese, yogurt, beer, wine etic
  - Some are used as probiotics with anti-inflammatory and anti-cancer activties

Pathophysiology

- Polymicrobial nature
  - One micro-organism might produce the enzyme necessary to cause coagulation of the vessels ➔ decreased blood supply ➔ hypoxia ➔ growth of facultative anaerobes/micro-aerophilic organisms ➔ release of enzymes (lecithinase, collagenase) ➔ digestion of fascial barriers ➔ NF

Risk factors

- • Diabetes
- • Chronic disease
- • Steroids
- • Age > 50 years
- • Malnutrition
- • Intravenous drugs users
- • Peripheral vascular disease
- • Renal disease
- • Underlying malignancy
- • Obesity
- Immuno-compromised patients, with some form of immune deficiency or underlying malignancy may have synergistic NF infection

Risk factor

- The use of NSAID has been impiicated as a contributing factor for NF
- In a retrospective study in France, it was found that there is a strong association between NSAIDs and severe NF, particularly in children with varicella

Clinical features

- Diagnosis is primarily **clinical** and a high degree of suspicion is required

- Findings

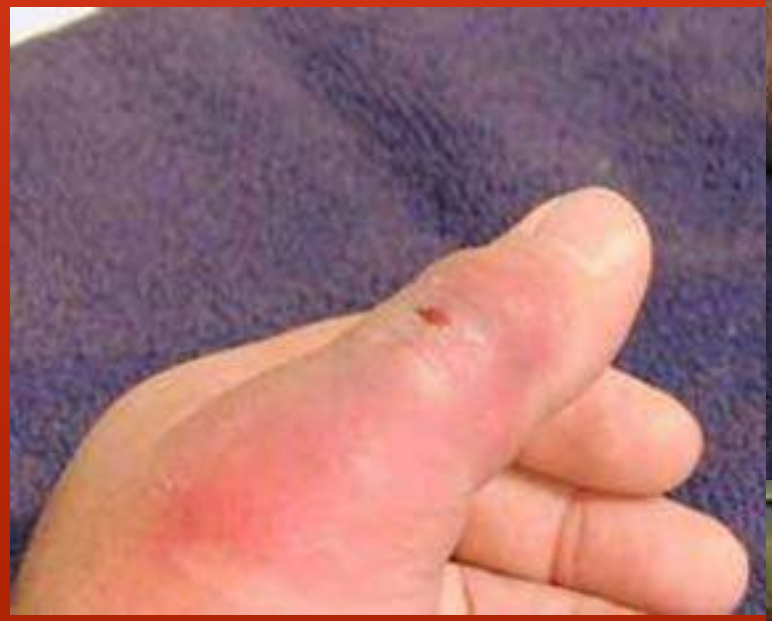
	%
Pain	100
Erythema	95
Oedema	82
Cellulitis	75
Fever	70
Discolouration	49
Crepitus	25
Vesicles	16

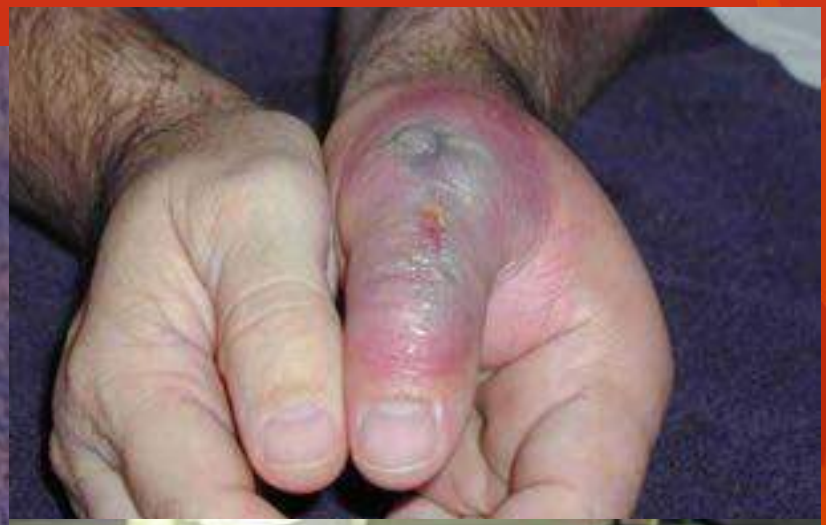
Clinical stages

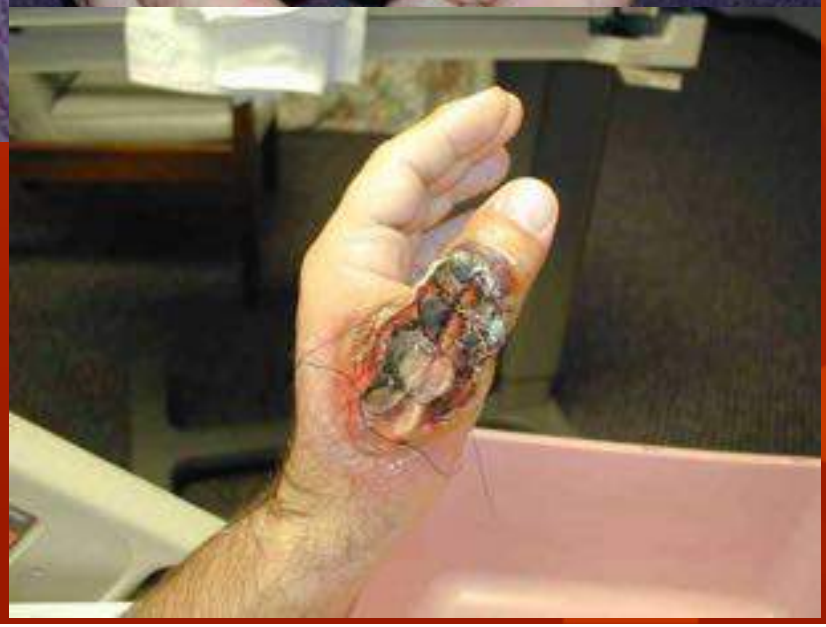
- As NF progresses, different clinical stages will be encountered
- Wang et al tried to devise a clinical staging according to the manifestations of cutaneous features

Stages	Clinical features
1 – Early	Tenderness beyond skin involvement
	Erythema
	Swelling
	Calor (warm skin)
2 – Intermediate	Blisters or bullae formation
3 – Late	Crepitus
	Skin anaesthesia
	Skin necrosis with dusky discolouration

Clinical stages







Clinical features

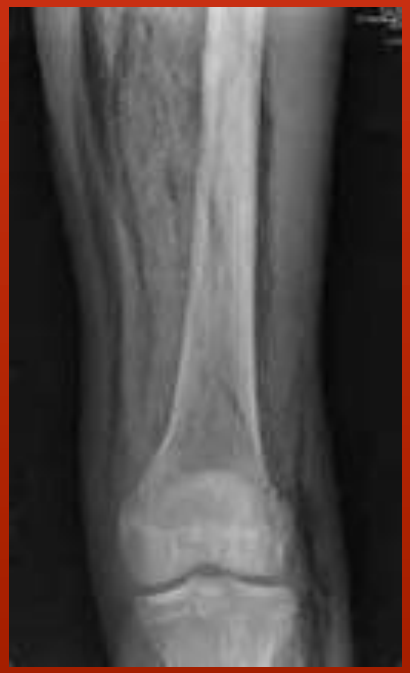
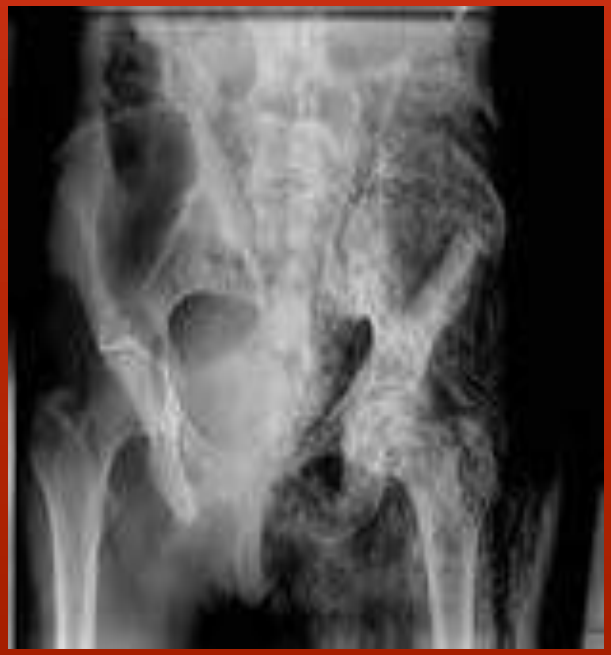
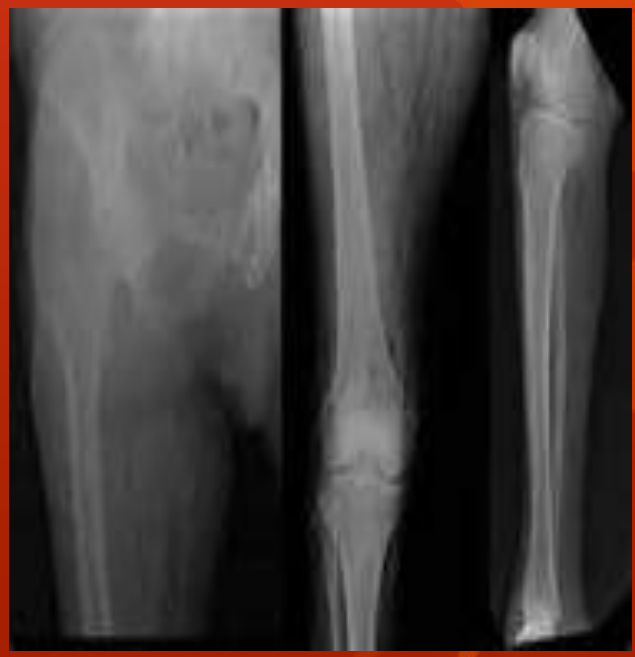
- Finger Test:
  - Finger test is initially described by Andreasen: A 2-cm incision is made under LA down to deep fascia. Probing to the level of superficial fascia is then performed. The lack of bleeding, foul-smelling ‘dishwater’ pus and minimal tissue resistance to finger dissection constitute a +ve finger test, which is diagnostic of NF

Radiological exam

- Overall, all radiographic modalities studied to date are limited by either low sensitivity or low specificity

- Plain XR can reveal subcutaneous gas or soft tissue swelling. But it is insensitive and not very valuable in the diagnosis of NF

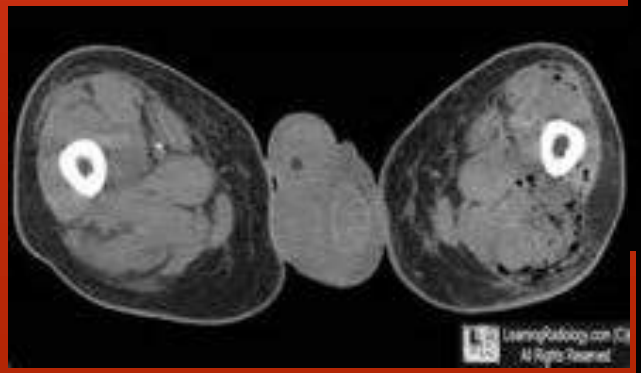
Radiological exam

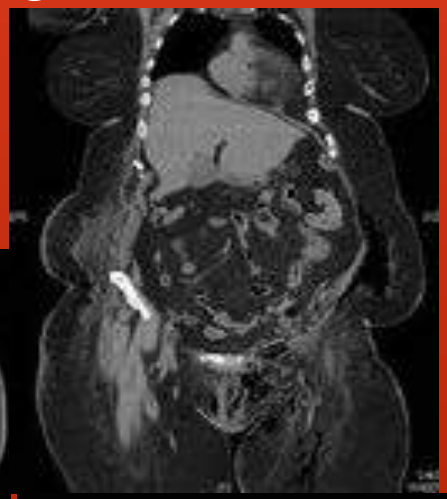




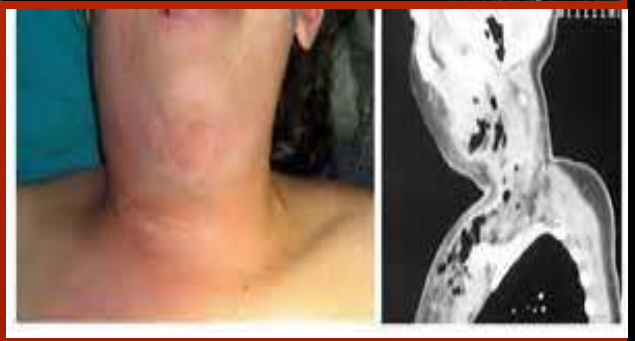
Radiological exam

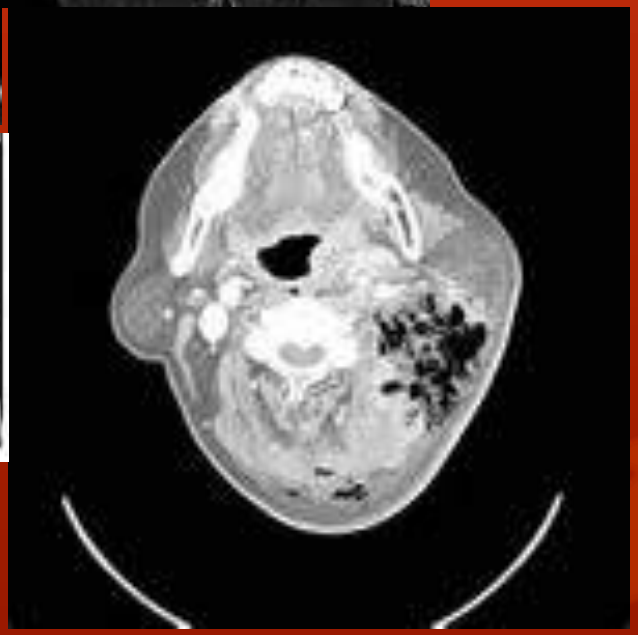
- CT scan is more sensitive because it can show fascial oedema and thickening, in addition to gas formation
- A retrospective study of 20 patients found that fascial thickening on CT scan had 80% sensitivity for NF and IV contrast added little benefit

Radiological exam





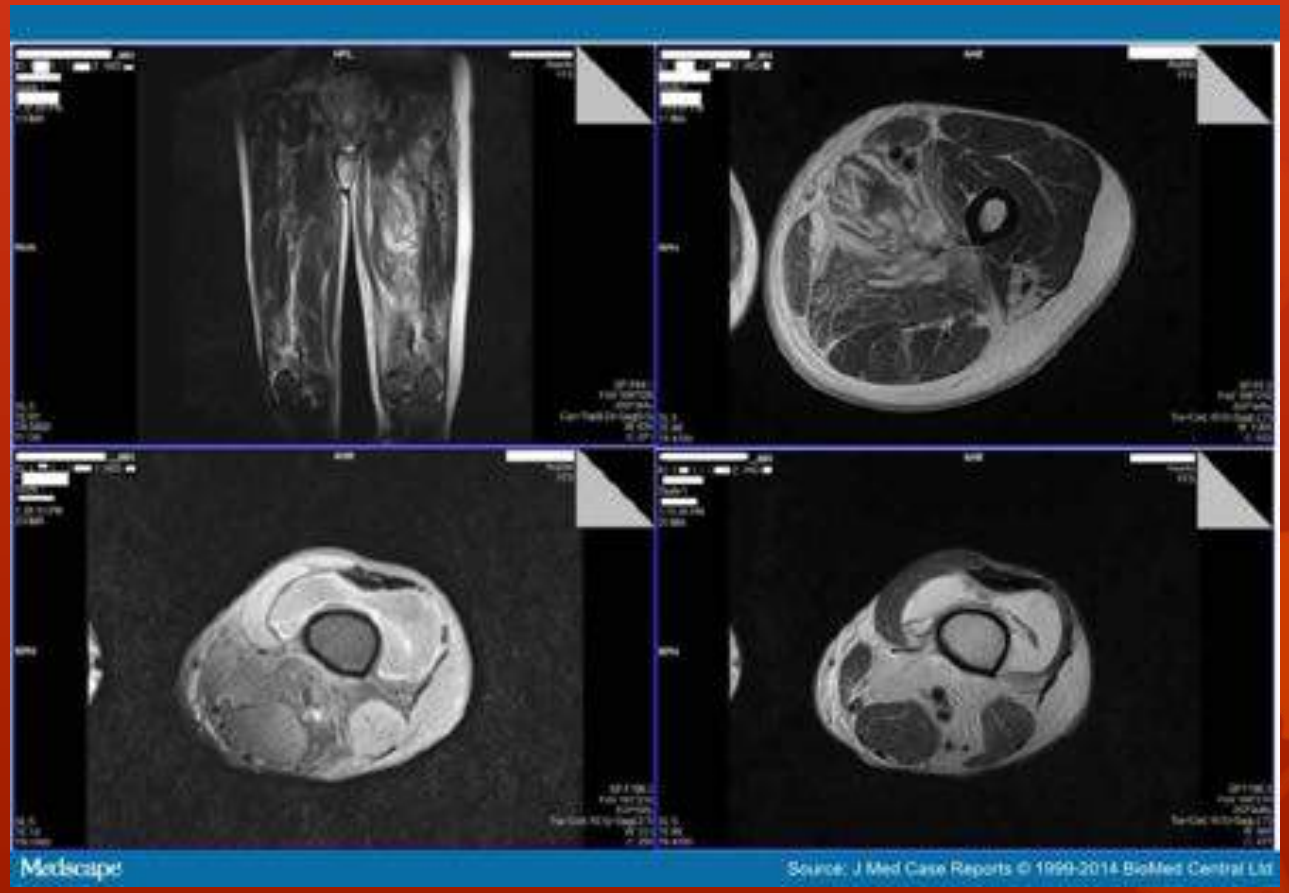




Radiological exam

- MRI scan has a high sensitivity of 90% but relative low specificity, from 50% to 85% for detecting NF
- Characteristic findings include soft tissue or fascial thickening on T2-weighted images with enhancement after contrast administration
- Findings that are more specific include hyperintense signals on T2-weighted images at the deep fascia and within muscles and peripheral enhancement on contrast-enhanced T1-weighted images

Radiological exam



LRINEC score

Value	LRINEC score, points
C-reactive protein, mg/L	
<150	0
>150	4
WBC count, cells/mm^3	
<15	0
15–25	1
>25	2
Hemoglobin level, g/dL	
>13.5	0
11–13.5	1
<11	2
Sodium level, mmol/L	
≥135	0
<135	2
Creatinine level, mg/dL	
≤1.6	0
>1.6	2
Glucose level, mg/dL	
≤180	0
>180	1

- Lab Risk Indicator for NF score
  - Developed by Wong et al in 2004
  - This involves a scoring system from using the parameters of CRP, total WBC, Hb, serum Na, serum Cr, and serum glucose levels

Risk category	LRINEC score, points	Probability of NSTI, %
Low	≤5	<50
Intermediate	6–7	50–75
High	≥8	>75

LRINEC score

- The probability of NF is 50 – 75% with a score of 6 or 7, and >75% with a score >/=8
- The model has a 92% positive predictive value and a 96% negative predictive value for detecting early stages of NF
- The LRINEC score has been validated in a number of studies. It is becoming the standard of investigation to diagnose NF in early clinical settings

Treatment

- Early diagnosis and surgical debridement
- Broad-spectrum antibiotics
- Aggressive resuscitation
- Frequent evaluation
- Comprehensive nutritional support

Treatment

- Surgical debridement:
  - The most important step because it is the fastest way to reduce bacterial load and stop the necrotic process
  - The goal of the surgery is to remove all the necrotic tissue, muscle, skin and fascia
  - Sometimes, amputation may be needed in advanced and aggressive infection
  - Usually a 2nd look debridement is required after the 1st 24 hrs to remove additional necrotic tissue due to impaired perfusion as well as ongoing infection

Treatment

- Wound coverage:
  - Once the infection has resolved and a viable healthy granulation tissue is obtained, the wound may be closed with either skin flaps or split-thickness grafts
  - Many cases may require reconstructive surgery with free tissue flaps

Treatment

- Antibiotics:
  - Initially, the infection should be treated empirically with broad-spectrum agents with activity against Gram+ve, Gram-ve, and anaerobic organisms until sensitivities are obtained
  - Clindamycin is advised if there is any clinical suspicion of GAS or Staphylococcus aureus because it shuts down the bacterial ribosome function, which inhibits both M protein and exotoxin production

Treatment

- Eagle effect:
  - Describes the limits of efficacy of penicillin after a streptococcal infection has reached the steady state but the efficacy of clindamycin is not affected by the size of the bacterial inoculum or the stage of growth

	Usual organisms	Preferred regimens	Alternatives	Special considerations / [usual duration of treatment]
Necrotizing fasciitis [171]				Immediate surgical intervention essential. Urgent consult clinical microbiologist.
1. Following exposure to freshwater; seawater or seafood	*Aeromonas hydrophila, A. caviae, Vibrio vulnificus*	I.V. fluoroquinolone + I.V. amoxicillin-clavulanate		
2. Following cuts and abrasion; recent chickenpox; IVDU; healthy adults	Group A streptococci	I.V. penicillin G + I.V. linezolid [172]		Add high dose IVIG (1-2 g/kg for 1 dose) for streptococcal toxic shock syndrome [173] *. In HK, Group A streptococci : more often resistant to clindamycin (50-80%) [170].
3. Following intra-abdominal, gynaecological or perineal surgery [174]	Polymicrobial: *Enterobacteriaceae*, streptococci, anaerobes	I.V. imipenem or meropenem	I.V. amoxicillin-clavulanate + levofloxacin	
Bite wound (animal	streptococci, S	Amoxicillin-	Penicillin V or	• Risk of infection after dog

Treatment

- Adjunctive therapies:
  - **IVIg (immunoglobuin)**
  - **HBO (hyperbaric oxygen)**

Treatment

- IVIG:
  - Found to inhibit the activation of T-cells by superantigens and inhibit the activity of streptococcal antigens to elicit cytokine production
  - It is postulated to have potential use to treat GAS
  - The typical dosage is 1 – 2g/kg of BW per day x 2 days
  - Its use is controversial. Some studies have reported reduced mortality but a recent review found no improved clinical outcomes in NF

Treatment

- Conditions for which HBO is useful:
  - Related to diving and compressed-air work
    - Decompression illness
    - Arterial gas embolism
  - Acute indications
    - CO poisoning
    - **Clostridial myonecrosis**
    - **Soft tissue NF**
  - Chronic indications
    - Radiation tissue damage
    - Refractory osteomyelitis
    - Enhancement of healing in selected problem wounds

Treatment

- HBO:
  - Its use in NF is highly controversial, only supported by anecdotal and retrospective reports
  - For polymicrobial infections, esp., involving Clostridium species, it switches off toxin production and is believed to increase the bactericidal action of neutrophils
  - It may help to identify infection boundaries, reducing unnecessary debridement
  - Standard therapy is 2 – 2.5 atm for 90 – 120 mins twice daily, then daily, up to 30 sessions until infection progression is halted
  - Have risks and complications: tympanic membrane rupture, seizures, and central oxygen toxicity

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Risk category	LRINEC score, points	Probability of NSTI, %
Low	≤5	<50
Intermediate	6–7	50–75
High	≥8	>75

Prognosis

- Anaya and colleagues created a score to categorise patients according to the risk of mortality

Table 3

Clinical score predictive of death for patients with necrotizing soft tissue infec

Parameter	Score
Heart rate more than 110 beats per minute	1
Temperature less than 36°C	1
Serum creatinine more than 1.5 mg/dL	1
Age more than 50 years	3
White blood cell count more than 40,000/mcL	3
Hematocrit more than 50%	3

Group category	Number of points	Percentage mortality
1	0–2	6%
2	3–5	24%
3	6 or more	88%

Take home messages

- High index of suspicion
- Early diagnosis
- LRINEC score
- Emergency surgical debridement
- Broad-spectrum antibiotics
- Resuscitation
- Wound coverage
- Nutrition and supportive care

Thank you