RESURGENCE OF
F. TULARENSIS IN BELGIUM?
Case report 1 (2012)

Healthy 25-year-old man, student LLN

✓ Travel in south of France (holidays) 6 months ago, not pets, play tennis.
✓ 3 weeks ago: fever, myalgia, fatigue. Amox-Clav by GP, without improvement.
✓ Bilateral conjunctivitis followed by a painful disseminated acneiform rash (arms, legs, buttocks, thorax and the face including the scalp).
✓ Febrile with night sweats, moderate altered status.
✓ Doxycycline (3d) prescribed by the GP due to the extension of the cutaneous lesions ➔ ID consultation
Case report 1:
Healthy 25-year-old man, student LLN, ID consultation

- Arthralgia (knees, ankles, elbows) with fonctionnel disability
- Decreasing rash and fever
- Right axillair-anterior painful lesion with local erythema.
- Remains an injury on his right index during hunting, later handled a dead wild boar.

- Suppurative lesion: Clonazone with a slow recovery.
Case report 1:
Healthy 25-year-old man, student LLN, ID consultation

- Physical examination: no fever, diffuse crusty healing cutaneous lesions and purple non-suppurative lesion on the right index finger.
- An inflammatory (3x5cm), erythematous and painful adenopathy on the anterior area of the axillary region.
- Biology: elevated CRP (94mg/l), WBC count of $10.9 \times 10^3/\mu l$ (66% PNL, 11% monocytes) with a normal platelet count.
Case report 1:
Healthy 25-year-old man, student LLN, ID consultation

- Doxycycline extended for 14 days, pending results for serology.
- Diagnosis confirmed by an ELISA (CERVA)
- Improvement with complete defervescence within the week, complete resolution of cutaneous lesions and decreasing of volume and inflammation of the adenopathy.
- 4 weeks later, recurrence of symptoms. Ciprofloxacin 750 mg bid for 21 days (skin fistula).
Case report 2 (2015)
68 years-old woman

ID consultation

✓ C2H5 abuse, no medication
✓ Altered status, mild recurrent fever and night sweats, fatigue, anorexia for 3 weeks.
✓ Index lesion « panari »: clonazone, staphycid/amox-clav, surgical debridement
✓ 2 subcutaneous painful nodules on the forearm
✓ 3 inflammatory painful adenopathies at elbow (2-2-1cm), one axillary (4cm)
✓ Elevated CRP and leucocytosis.
Case report 2 (2015)
65 years-old woman, pensionnée

ID consultation

✓ 4 weeks ago, got an index wound during gardening
  ✓ garden plowed by wild boars (Wépion)

✓ Cutaneous nodule biopsy

✓ Clinical suspicion, confirmed by serology
  ✓ Biopsy: non necrotizing granulomatous lesion

✓ Ciprofloxacin 3 weeks, with improvement
  ✓ Recurrence 3 weeks after cessation of AB (axillary adenopathy)
    ✓ New treatment of 3 weeks, no recurrence
2 others cases (2013-2014)

✓ 39-years-old farmer, hunter
  • Ulcero-glandular presentation
  • Bite on the knee, cutaneous lesion
  • Inguinal adenopathy, general malaise with fever
  • 2 weeks of doxy

✓ 30-years-old man, trailer
  • Ulcero-glandular presentation (inguinal adenopathy)
  • Wound on the left knee, cutaneous chronic lesion
  • General malaise with fever
  • 3 weeks ciprofloxacin
    • acneiform/maculo-papulous eruption at d1
**F. tularensis: Microbiology**

- Facultative intracellular bacterium
  - Aerobic Gram-negative coco-bacilli
- Family Francisellaceae
  - 2 species in the genus *Francisella*
    - 4 subspecies of *F. tularensis*: tularensis, holarctica, novicida, mediasiatica
**F. tularensis**: Phylogenia

✓ **F. tularensis and holarctica:**

- **Main subspecies associated with human diseases**
  - *F.T. tularensis*: most virulent, mainly described in North America
  - *F.T. holarctica*: less virulent, predominantly found in Asia and in Europe (but also in North America)

*Nature Rev Microbiol 2004, Petra*
F. tularensis: Epidemiology

- Firstly described in the County of Tulare, California,
  - by McCoy and Chapin in ground squirrel with a plague-like illness (1911)
  - then isolated and cultivated by Dr. Edward Francis (1919)

- Reservoirs:
  - Infect hundred of different vertebrates and invertebrates
  - no more than dozen mamalian species are important to its ecology
    - predominantly lagomorphs and rodents (voles, squirrels, muskrats, hares, ...).
  - bloodfeeding arthropods and flies are also important vectors for animals and human diseases.
F. tularensis: Epidemiology

- In Europe, endemic foci vary significantly
  - Scandinavian countries report high number of cases annually (Sweden, Finland)
  - Fewer cases are reported in central and southern Europe (France, Hungary, Austria, Czech republic, Germany, Spain)

- It re-emerged in the early 21st century
  - in Turkey, Bulgaria, Kosovo, Georgia
  - with many outbreaks reported (France, ...)

- in Belgium since 1950
  - only 3 other cases were reported
    - data from Coda-cerva, only one clinical report
    - 4 cases in CHU between 2012-2015

- Agent of bioterrorism
F. tularensis: Epidemiology

Disease is endemic or potentially endemic to 46 countries

Annual Disease rates per 100,000 population

- Not Endemic
- >0 to 0.01
- >0.01 to 0.04
- >0.04 to 0.1
- >0.1 to 0.4
- >0.4
F. tularensis: Epidemiology

**Figure 3**
Incidência de tularemia por região de residência dos casos, França 2002-2012

In Euro Surveill. 2014;19(45):pii=20956.

Mean annual incidence per million inhabitants from 2002 to 2012

INVS sept2015
F. tularensis: Pathogeny

- Survives few days in the environment if over 10°C
  - but many months in water, mud, straw, ... below 0°C.

- Infectious dose in human depends on the portal of entry (and subsp.):
  - 10-50 organisms intradermally or when inhalated
  - $10^8$ organisms when ingested

- Penetration:
  - mainly through sites of inapparent skin disruption
  - reported to penetrate intact skin
**F. tularensis: Pathogenicity**

**Tularemia** (tu-lar-e´me-a) Tulare county, California where discovered

**Definition:** An acute, infectious disease of wild rabbits and rodents caused by the bacterium, *Francisella tularensis*; also known as rabbit fever.

- The bacterium *F. tularensis* may be transmitted between rodents and rabbits and to humans by ticks.
- Drinking contaminated water.
- Contact with infected animals.
- Eating undercooked rabbit meat.
- Inhaling contaminated dust.
F. tularensis: Epidemiology

F. tularensis: Clinical disease

- Depends on
  - the virulence of the strain
  - the portal of entry
  - the extent of systemic involvement
  - the immune status of the host
  ➔ from asymptomatic to acute sepsis and death (rare F. t. holartica)
- Incubation period: 3-5 days (vary from 1 to 21 days)
- Systemic symptoms
  - start abruptly: fever, chills, headache (flu-like sdo)
  - less virulent strains cause a milder, self-limited disease that may resolve without therapy.
F. tularensis: Clinical disease

☑️ 6 classic forms of tularemia, with some overlaps in many patients

- Ulcero-glandular tularemia
- Glandular tularemia
- Oculo-glandular form
- Oropharyngeal disease
- Pulmonary tularemia
- Systemic disease: typhoidal tularemia
**F. tularensis: Ulcero-glandular disease**

- Most common form in central Europe
- After a cutaneous inoculation, *F. tularensis* multiply locally and produces a papule
  - 2-4 days later ulceration spread to regional lymph nodes lymphohematogen dissemination
- The skin lesion may appear before, simultaneously with or several days after the adenopathy.
  - skin lesion and adenopathy are painful
  - If untreated, ulceration may take weeks to heal in a residual escar and adenopathy can become fluctuant or fistulated
  - Location of the ulcer generally reflects the mode of contamination:
    - hands and forearms: animals or environmental contact
    - trunk, lower extremities, head and neck: suggests insects bites
**F. tularensis: Other glandular diseases**

- **Glandular disease**: the 2nd most common
  - but the first in children
  - with single or multiple adenopathy without skin lesion
  - mode of acquisition is similar than ulcero-glandular disease.

- **Oculoglandular presentation**: 
  - occurs when *F. tularensis* gains access to the conjunctiva
  - symptoms include conjunctivitis with regional adenopathy (*Parinaud’s oculoglandular syndrome*)
F. tularensis: Oropharyngeal disease

✓ Oropharyngeal disease is rare in USA/central europe
  • frequently reported in outbreaks in some countries
    • Kosovo, Turkey
  • following ingestion of contaminated food or water,
  • fever and severe sore throat with exsudative tonsillitis or pharyngitis (frequently ulcerated) and cervical lymphadenopathies
F. tularensis: Typhoidal tularemia

✓ 5-30% of cases

- is a febril illness without regional adenopathy or others localizing signs.
- the most difficult to diagnose
  - clinical presentation ranging from acute sepsis to chronic illness.
  - chronic underlying conditions are frequently reported.
  - it can results of any portal of entry.
- Major symptoms:
  - high and prolonged fever, headache, myalgia, sore throat, anorexia.
  - Diarrhea, a major manifestation only in typhoidal tularemia
    - watery and loose.
  - Secondary pulmonary involvement is reported in up to 45% of cases.
F. tularensis: Pulmonary disease

✓ More common in adults patients (up to 25% of cases)
  
  - It results from direct inhalation of the bacteria or from secondary hematogenous spread to the lung.
  - Pneumonia due to F. tularensis subsp. tularensis is more severe than that caused by subsp. holarctica, but disease may be prolonged in both cases
F. tularensis: Secondary manifestations

✓ Secondary skin manifestation: frequent ≈ 30%

- many forms such as
  - maculo-papular or vesiculopapular eruption,
  - erythema multiforme (*typhoidal tularemia*),
  - pustules, acneiform lesions, urticaria,
  - erythema nodosum (*most commonly with pneumonic tularemia, typhoidal tularemia*),
  - sweet syndrome

- usually appearing within the first 2 weeks of symptoms
F. tularensis: Diagnosis

- Based on clinical suspicion with epidemiological history
- Routine lab tests are non specific
- Microbio lab:
  - rarely seen in Gram stained smear or tissue biopsy
  - does not grow in routinely plated culture
  - can be recovered from any liquid of tissue if processed in supportive media
  - High virulence and transmissibility: a biosafety level 3 is required to process isolates suspected of being infected
**F. tularensis: diagnosis**

- **Serology**: most common way to the diagnosis *(Coda-cerva)*
  - Agglutination, microagglutination, ELISA *(F. t. tularensis/holarctica)*
  - Usually negative the 1rst week of symptoms but (+) in most patients after 2 weeks and peak after 4-5 weeks.
    - A presumptive diagnosis: an acute agglutination titer of $\geq 1/160$ or an acute microagglutination $\geq 1/128$.
    - IgM and IgG appear together and high titers may persist for long time.
      - Definitive diagnosis $\geq 4x$ in titer between acute and convalescent serologies (10 days).
    - Cross reactions is reported with *Brucella sp, Yersinia sp* and *Proteus OX19*

- **PCR**: Not commonly available
  - Coda-cerva, subtypes identification
**F. tularensis: Treatment**

- **Streptomycin** 7.5-10 mg /kg/12h IM (adult, up to 2g/d)
  - Excepted in meningitis
  - High rate of cure, low rates of relapses
  - Gentamicin od (3 à 5 mg/k, peak ≥5,0 μg/ml) as alternative
  - 7-10 days, up to 14d in more severe case or if response to treatment is delayed

- **Chloramphenicol is effective**

- **Tetracyclines** is an alternative, but 14d required and more relapses reported (up to 15%) (doxy 200mg/d)
F. tularensis: Treatment

✓ Good in vitro susceptibility to fluoroquinolone
  • subsp. holarctica (few data available for tularensis subsp.)
  • considered by some as the drug of choice in mild or moderate tularemia
    • for at least 10-14 days
    • Some relapses
**F. tularensis: Resurgence?**

- Many European countries published an increasing number of cases, including in non-endemic areas.
- Increasing incidence possibly related to:
  - Expansion of the animal reservoir (rabbits, rodents), climate change?
  - Importation of infected game animal from Eastern Europe
  - Arthropod vectors proliferation (ticks)?
  - More frequent contact with the natural reservoirs during outdoor activities?
  - Water/food contamination (Turkey)
  - Combination of these factors
  - More reported?
Only 3 cases diagnosed in Belgium since 1950 …
- 4 cases in 3 years at MontGodinne (+1)
- Underdiagnosed disease in higher risk area?

Diagnosis has to be evoked
- Febrile illness with adenopathy +/- skin lesion, +/- eruption
- With an incubation period of 3-5d, non responding to classical antibiotic
- With epidemiological risk factors
  - outdoor activities, hunting, tick bites

Human surveillance and evaluation of animal reservoir
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