PROGETTO PANDORA ID-22

LE MICOBATTERIOSI NON TUBERCOLARI

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VIRTUAL EDITION

Le infezioni extra-polmonari da micobatteri non tubercolari

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VILLA MARELLI

stop TB

Introduzione

Over the past several years, the prevalence of human disease caused by nontuberculous mycobacteria (NTM) has increased. Whether the increase in cases is real or whether more cases are being recognized remains unclear.

Despite a considerable increase in knowledge about NTM infections, they still represent a diagnostic and therapeutic challenge for several reasons:

1) pathogenic isolates may be indistinguishable from contaminant or saprophytic isolates;
2) timely and reliable identification of isolates may depend on proper communication between clinicians and laboratory staff;
3) lack of standardized susceptibility testing makes adoption of tailored therapies unrealistic;
4) lack of treatment guidelines exposes patients to toxic drugs and disappointing outcomes. Laboratory research and multicenter controlled trials are needed to improve diagnosis and treatment of these infections.

Reservoirs

NTM are ubiquitous environmental organisms present in soil and water systems.

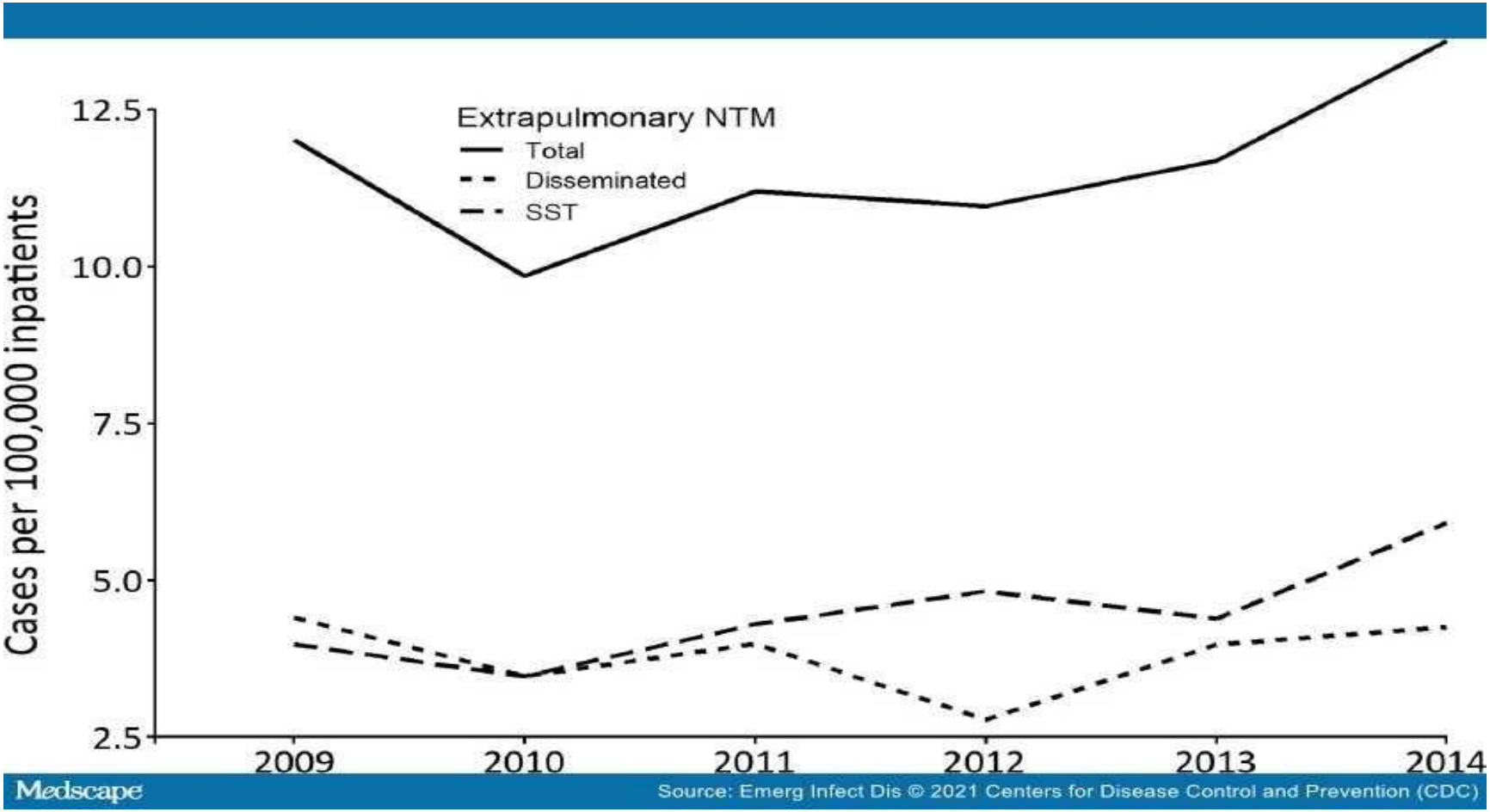
NTM thrive within drinking water systems and inhabit the biofilm present in water pipes:

- plumbing systems and hot water tanks
- shower heads and faucets
- whirlpool spas and footbaths
- respiratory therapy equipment
- humidifiers

NTM is also present in soil including:

- potting soil
- peat moss

Andamento temporale delle forme di NTM-EPD negli USA



Modes of Transmission

- Patients with localized extrapulmonary disease typically acquire disease as a result of trauma or a medical or health-related procedure whereby tap water or other contaminated products are directly inoculated into the skin.
- Examples would include whirlpool footbaths or hot tubs, contaminated tattoo ink, surgical procedures where tap water or other contaminated solutions inadvertently entered the surgical field, or injections where injectable material was contaminated.
- These infections occur sporadically (e.g., trauma), but also occur as small clusters (e.g., surgical infections) and outbreaks (e.g., tattoo-related infections from contaminated ink products), depending upon the vehicle of contamination.
- Acquisition of NTM in those with disseminated disease is thought to be through ingestion of the organism.

NTM-PD vs NTM-ePD

- Individuals susceptible to extrapulmonary NTM diseases differ greatly from those with pulmonary disease in terms of both prevalence and associated risk factors.
- In one Korean study,
  - species commonly isolated from pulmonary specimens were
    - Mycobacterium intracellulare (38.9%)
    - M. avium (23.1%)
    - M. abscessus (8.4%)
    - M. kansasii (7.7%);
  - while common extrapulmonary specimens were
    - M. avium (25.0%)
    - M. fortuitum complex (20.9%)
    - M. intracellulare (16.6%)

Baseline Characteristics of 117 patients with NTM-ePD in Korea

Variables N (%)

- Age (years) 53.1 15.6
- Female sex, n (%) 71 (60.7)
- **Comorbidities, n (%)**
- Diabetes mellitus 24 (20.5)
- HIV infection 1 (0.9)
- Solid organ cancer 10 (8.5)
- Hematologic malignancy 4 (3.4)
- History of previous tuberculosis 6 (5.1)
- Chronic kidney disease 14 (12.0)
- Chronic liver disease 4 (3.4)
- Connective tissue disease 5 (4.3)
- Immunosuppressive treatment 16 (13.7)
- Antibiotics treatment within 30 days 40 (34.2)

Predisposing factors, n (%)

- Any surgery 20 (17.1)
- Orthopedic Surgery 4 (3.4)
- Plastic surgery 4 (3.4)
- Other surgery 12 (10.3)
- Local injection 17 (14.5)
- History of acupuncture 6 (5.1)
- Trauma 6 (5.1)
- Indwelling catheter 4 (3.4)
- Unknown 64 (54.7)

Laboratory findings

- ESR (mm/h) 33.0 (16.0–57.0)
- CRP (mg/L) 11.55 (2.90–57.05)
- IGRA positivity, n (%) 11/23 (47.8)

Characteristics, clinical outcomes, and predisposing factors for 134 cases of extrapulmonary nontuberculous mycobacteria (NTM) infections — Oregon, 2014–2016

- **No. (%)**
- **Total cases 2014–2016** **134 (100)**
- 2014 45 (34)
- 2015 44 (33)
- 2016 45 (34)
- **Sex**
- Female 70 (52)
- Male 64 (48)
- **Race**
- White 96 (72)
- Asian/Pacific Islander 9 (7)
- Other or multiple 6 (4)
- Black 2 (1)
- American Indian/Alaska Native 1 (1)
- Unknown 20 (15)
- **Ethnicity**
- Non-Hispanic 96 (72)
- Hispanic 12 (9)
- Unknown 26 (19)
- **Outcome**
- Hospitalized (130) 43 (33)
- Sepsis (123) 18 (15)
- NTM-related death 1 (1)
- **Predisposing factor***
- Worked with potting soil (98) 41 (42)
- Immunocompromised (124) 42 (34)
- Surgery (120) 32 (27)
- Outpatient infusions or injections (110) 24 (22)
- Skin trauma (107) 21 (20)
- Immunosuppressive therapy (120) 23 (19)
- Hot tub or spa use (104) 16 (15)
- Acupuncture (106) 13 (12)
- Fish tank maintenance (104) 9 (9)
- Nail salon visit (103) 7 (7)
- Fish handling (105) 6 (6)
- Tattoo receipt (108) 2 (2)
- **>1 Predisposing factor† (124) 84 (68)**

Localizations of disease

- Extrapulmonary NTM disease manifests as cutaneous, bone, joint, lymph node, or central nervous system (CNS) disease.
  - Cutaneous infections typically result from either direct inoculation during trauma, surgical or medical procedures, exposures to whirlpool baths, or other settings such as nail salons or tattoo procedures.
  - Isolated lymphadenitis occurs in otherwise healthy children, generally <5 years of age.
  - Disseminated extrapulmonary disease generally only occurs in immunocompromised patients (e.g., HIV, transplant, cancer, end-stage renal disease, others) and typically results from infection via the gastrointestinal tract with hematogenous spread of organism.

Extrapulmonary Confirmed Case Definition

- Patients with signs and symptoms referable to the area and NTM species or complex determined by culture or by molecular methods, that is not *M. tuberculosis complex , M. gordonae, or M. leprae.*
- Include the following sites:

  1. Skin or soft tissue from wound or abscess
  2. Lymph node
  3. Urine
  4. Normally sterile sites including blood, spinal fluid, bone marrow, abdominal or pleural fluid, bone

- Exclude cultures from lower respiratory samples such as sputum, bronchial alveolar lavage, tracheal aspirates or lung tissue

Extrapulmonary Presumptive Case Definitions

- Patients with signs and symptoms referable to the area and culture or molecular evidence of infection by a mycobacterial species known not to be an M. tuberculosis complex organism but lacking species or complex determination. Include the following sites*:*

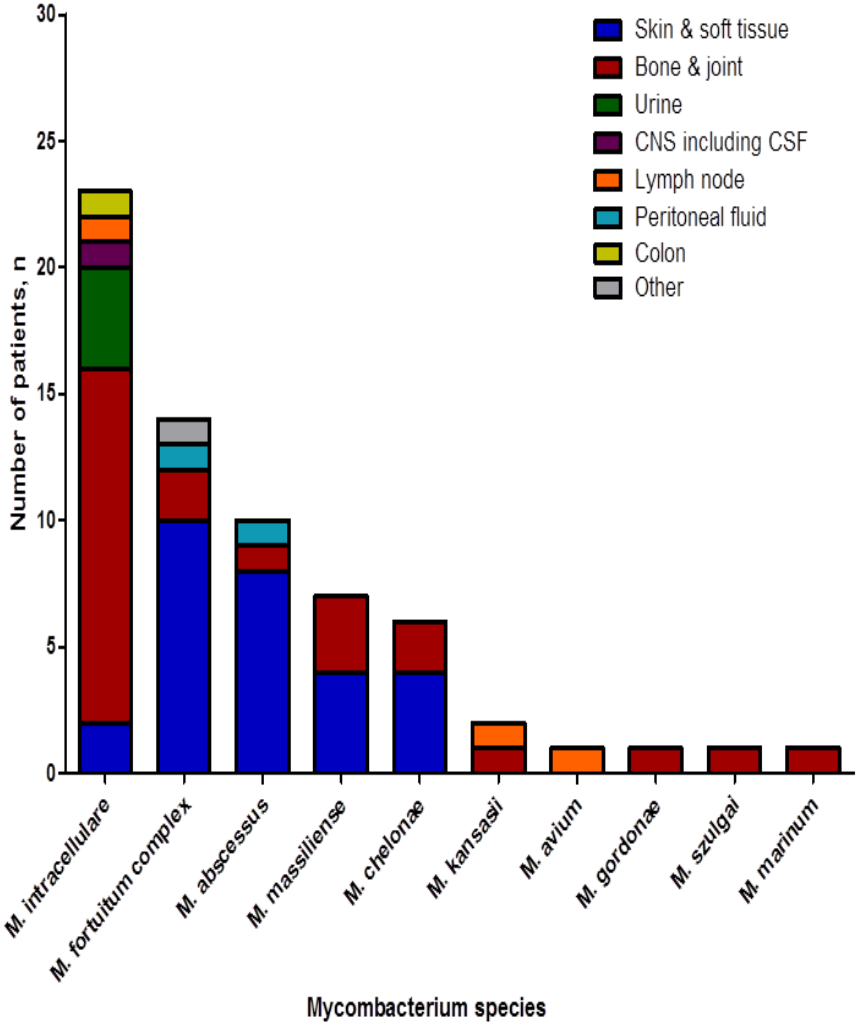
  1. Skin or soft tissue from wound or abscess

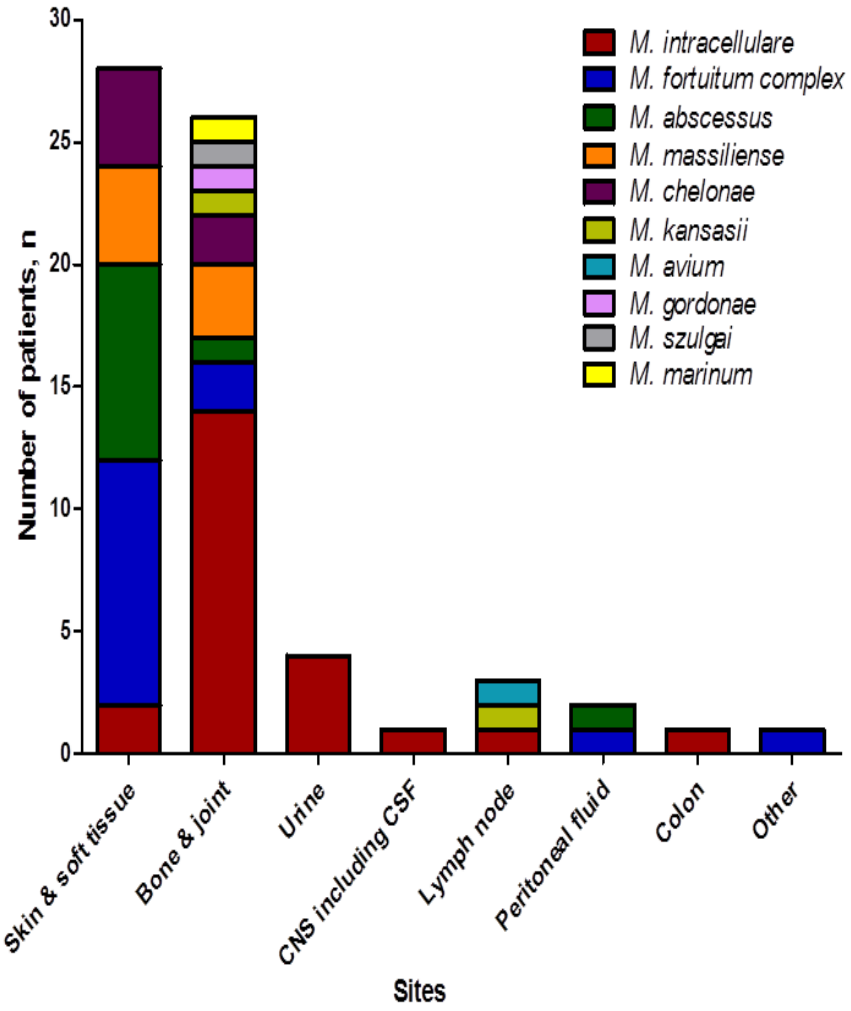
  2. Lymph node

  3. Urine

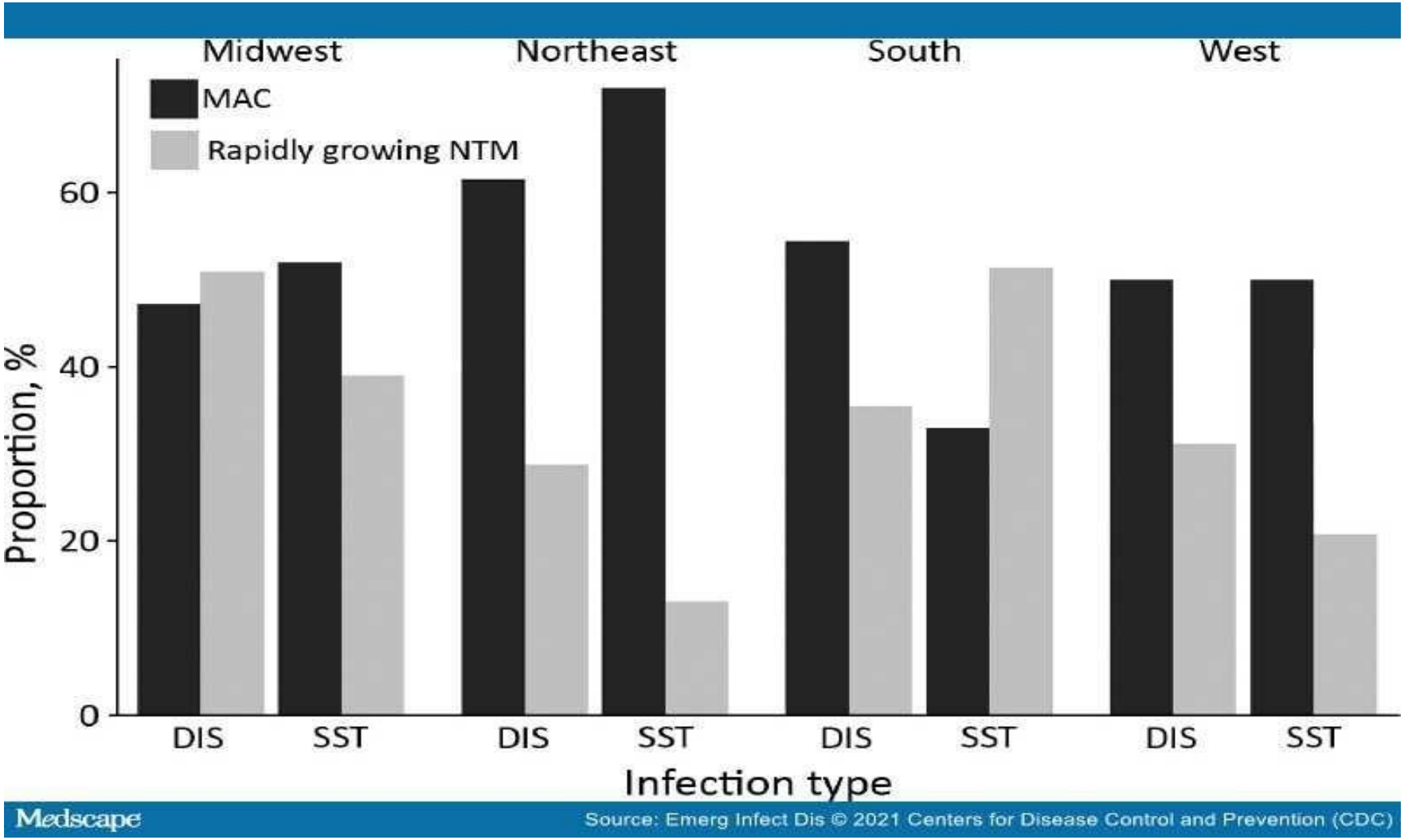
  4. Normally sterile sites including blood, spinal fluid, bone marrow, abdominal or pleural fluid, bone

Species and site of infection of nontuberculous mycobacteria isolates in 117 Korean Pts.



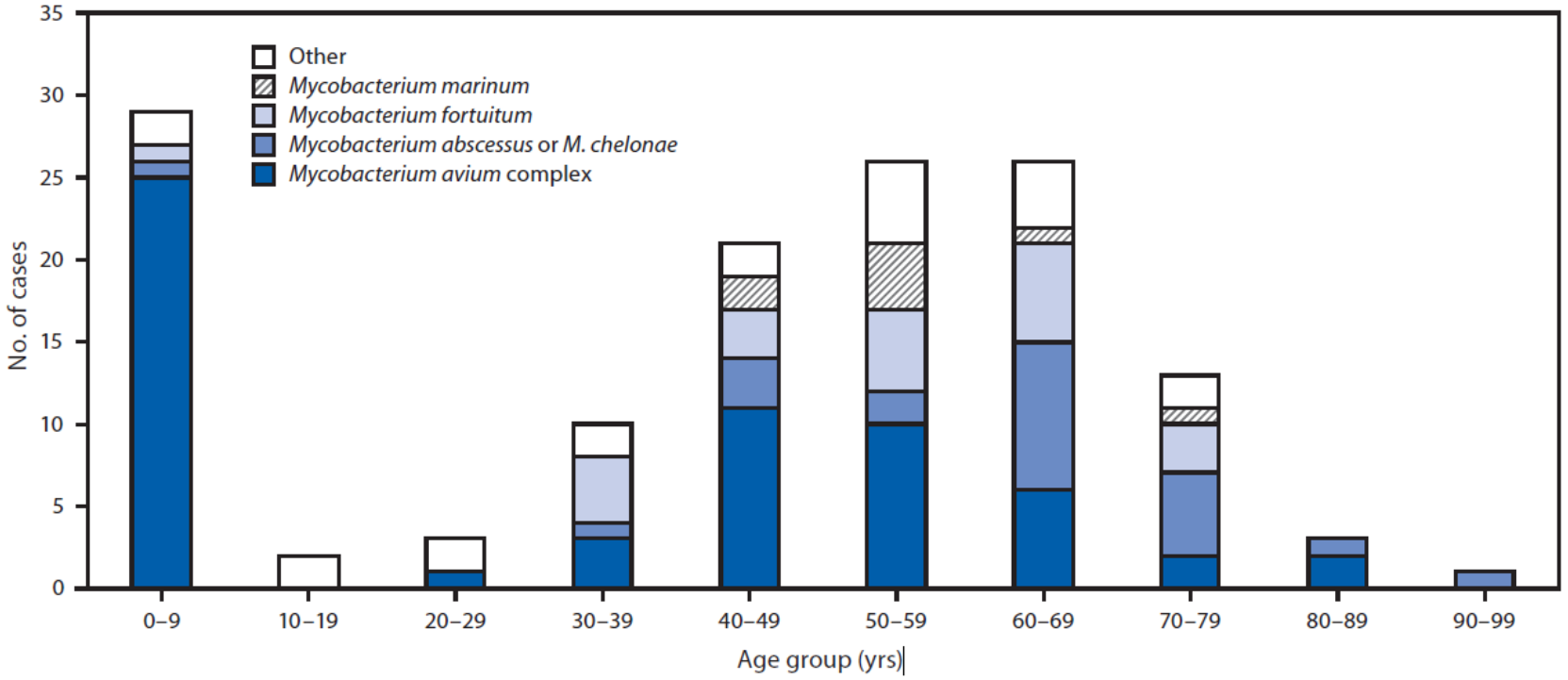


Distribuzione per area geografica, tipologia di NTM e localizzazione di malattia- USA



Nontuberculous mycobacteria (NTM) species identified in cases with extrapulmonary NTM infections, by age group — Oregon, 2014–2016

FIGURE. Nontuberculous mycobacteria (NTM) species identified in cases with extrapulmonary NTM infections, by age group — Oregon, 2014–2016



Villa Marelli 2000-2022

- 699 NTM-D
  - 582 NTM-PD
  - 15 NTM-P/EPD
  - 102 NTM-EPD
    - ORL 74 (70 >18 aa)
    - LN (addome, inguine, ascella) 10
    - Cute+Tessuti molli 6
    - Disseminata 5
- Ossea 3
- Urologica 3
- Prot. Valvolare 1

Villa Marelli 2000-2022

- 27 NTM-EPD adulti
  - M avium 9
  - M xenopy 4
  - M chelonae 3
  - M kansasii 2
  - M abscessus 1
  - M malmoense 1
  - M conceptionense 1
  - M sherrisi 1
  - M smegmatis 1
  - M chimaera 1
  - M senegalense 1
  - M fortuitum 1
  - M atipico? 1

Chimaera

- In addition, international outbreak of invasive cardiovascular infections with Mycobacterium chimaera occurred due to contaminated water tanks of heater–cooler units used during open-chest heart and vascular surgery

Timing of onset

Incubation Period

- Cutaneous disease typically manifests 2–10 weeks (median 3 weeks), but sometimes longer, after exposure or inoculation.

Period of Communicability

- NTM is generally not transmissible from person to person.

ROUTINE CASE INVESTIGATION

Extrapulmonary NTM

- All patients with extrapulmonary NTM isolates should be contacted. For all patients, investigators should solicit details as to both site(s) infected and potential sources of infection including:
- recent exposure (within 3 months) to whirlpool,
- footbaths at nail salons,
- recent surgical or injection procedures,
- fish tank exposure or fish handling,
- recent tattoo exposure,
- intravenous lines or catheters,
- other exposures in the preceding three months where water or soil sources could have infiltrated cutaneous tissues.

ROUTINE CASE INVESTIGATION

Extrapulmonary NTM

- Unless circumstances suggest a possible outbreak, further investigation is not indicated.
- Identification of a nosocomial (healthcare-acquired) case warrants additional case finding at the implicated institution as outbreaks have been reported in such institutions associated with environmental sources of exposure.

CONTROLLING FURTHER SPREAD

- No prophylaxis is indicated for contacts.
- If a cluster of cases is identified linked to a common environmental source, further environmental investigation and source control are warranted
- If a cluster of NTM is suspected, confirmation and investigation are warranted, so reservoirs may be found and eliminated.
- Contact epidemiologists to discuss possible outbreaks. Such investigations may involve questionnaires and detailed environmental evaluations.

Clinical Manifestations

- Localized soft tissue infection, at a surgical site or wound, for example, typically results in purplish nodules that typically drain pus and later can ulcerate or scar. Nodules frequently occur in multiples, and can be connected via subcutaneous fistulous tracts.
- Lymph node disease results in large, reddened, and tender nodes which also can ulcerate or drain pus. Chains of lymph nodes may become involved.
- Symptoms of disseminated extrapulmonary disease include dyspnea, fatigue, weight loss, fever, failure to thrive in children, night sweats, neurological manifestations and sepsis.

Skin and Soft Tissue Infections

SKIN AND SOFT TISSUE INFECTIONS

- These infections usually develop after traumatic injury, cosmetic procedures, or surgery, which can expose wounds to soil, water, or medical devices contaminated with environmental mycobacteria.
- Previous report has suggested that incidence of cutaneous NTM infection has increased nearly 3-fold during the past 30 years.
- RGM associated more with cosmetic and surgical procedures, whereas slow growing mycobacteria (SGM) infections were limited to patients with traumatic injuries.
- RGM often present with single-site rather than multisite infections.

SKIN AND SOFT TISSUE INFECTIONS

Although the epidemiology and clinical presentations of NTM responsible for skin and soft tissue infections differ, some species (MAC, *M. kansasii, M. xenopi, and M. marinum)* have been reported worldwide, whereas others (*M. ulcerans)* have limited geographic distribution.

Table 3. Skin and soft tissue infections caused by rapidly growing mycobacteria

Type of infection or procedure	*Mycobacterium* spp.	Clinical findings
Posttraumatic wound infections	*M. fortuitum, M. chelonae, M. abscessus, M. wolinskyi, M. goodii, M. porcinum*	Subcutaneous abscesses, cellulitis
Pedicures	*M. fortuitum, M. chelonae, M. mageritense*	Furunculosis
Subcutaneous, intraarticular, or periarticular Injections	*M. chelonae, M. abscessus*	Subcutaneous abscesses, painful nodules, multiple sinus tracts, joint infections, fever, chills after injection
Acupuncture	*M. abscessus, M. chelonae, M. nonchromogenicum*	Erythematous papules, nodules, ulcerative lesions, abscesses, confluent plaques, draining sinus tracts with discharge, wrist tenosynovitis
Cardiac surgery	*M. peregrinum, M. fortuitum, M. fortuitum* (third biovariant) *complex, M. wolinskyi, M. goodii, M. abscessus*	Sternal wound infection, endocarditis
Cosmetic surgery or other surgical procedures: liposuction, liposculpture, face lift, breast lift (reduction augmentation), silicon injection	*M. fortuitum, M. chelonae, M. chelonae, M. porcinum, M. wolinskyi, M. goodii*	Erythema, tenderness, nodules, skin induration, subcutaneous or deep-tissue abscesses, fever, malaise, multiple abscesses along original suction tracts, draining sinus tracts, local pain, swelling
Nipple piercing	*M. fortuitum, M. abscessus*	Asymptomatic nodules, tender nodules
Implanted with prosthetic material	*M. abscessus, M. goodii*	Abscesses
Pacemaker placement	*M. fortuitum, M. abscessus, M. wolinskyi*	Abscesses
Peritoneal dialysis catheter	*M. abscessus*	Abscesses

M. ulcerans

- *M. ulcerans* is the causative agent of *Buruli ulcer,* a disease reported in >30 countries, mainly in tropical and subtropical regions of Western and Central Africa but also in Central and South America, Southeast Asia, and the Western Pacific region.
- Currently limited knowledge is mainly the result of a low number of reported cases and inadequate surveillance.
- Recently studies conducted in some areas in which *M. ulcerans* is highly endemic have reported infection rates higher than those for either tuberculosis or leprosy.

Lymphadenitis

Generally, NTM adenitis is an indolent disease; most patients are otherwise healthy and have as their sole clinical sign a chronic neck mass that does not respond to antimicrobial drug therapy.

The disease is usually unilateral and occurs in the cervical, submandibular, or preauricular lymph nodes, although parotid and postauricular node involvement has been reported.

The nodes enlarge and may rapidly soften and rupture, forming a draining sinus.

Although spontaneous regression has occasionally been described, healing usually occurs by fibrosis and calcification.

Pyogenic and tuberculous adenitis are the most important differential diagnoses.

Lymphadenitis

Although a presumptive diagnosis of nontuberculous mycobacterial adenitis can be made on the basis of clinical history and physical examination, definitive diagnosis depends upon the recovery of mycobacteria.

In countries with low prevalence of TB, usually children aged under 2 (or 5) yrs have NTM disease, while older or immigrant children are more often affected by TB

Every effort should be made to obtain material for culture and further identification. Cultures of draining and ulcerated lesions, especially when swabs are used for specimen sampling, have been shown to give a lower diagnostic yield than do needle aspirates or tissue biopsy samples.

Histologic appearance of necrotizing granulomatous inflammation with various degrees of caseation is also diagnostic.

Osteoarticular Infections

NTM infections involving the musculoskeletal system are uncommon. However, when they do occur, both rapid and slow-growing species have been implicated in chronic granulomatous infections involving tendon sheaths, bursae, bones, and joints.

These are usually acquired by direct inoculation of the pathogen from an environmental source or a contiguous infection focus as a consequence of surgical procedures, penetrating trauma, injuries, or needle injections.

Most affected patients are immunocompetent, but some mycobacterial species, such as *M. chelonae and M. hemophilum,* are almost entirely recovered from patients with serious underlying diseases (HIV infection, immunosuppressive therapy, or blood disorders)

Osteoarticular Infections

Clinically, osteoarticular infections caused by NTM are indistinguishable from tuberculosis-associated infections.

Signs and symptoms:

- localized pain (with or without neurologic impairment)
- joint stiffness and swelling
- Lowgrade fever, sweating, chills
- anorexia, malaise, and weight loss
- Suppuration followed by extensive necrosis of the synovial tissue (rare)

More severe cases infection may extend to the periosteum and lead to osteomyelitis.

The clinical course of the disease is typically protracted: average time from onset of symptoms to diagnosis may be as long as 10 months.

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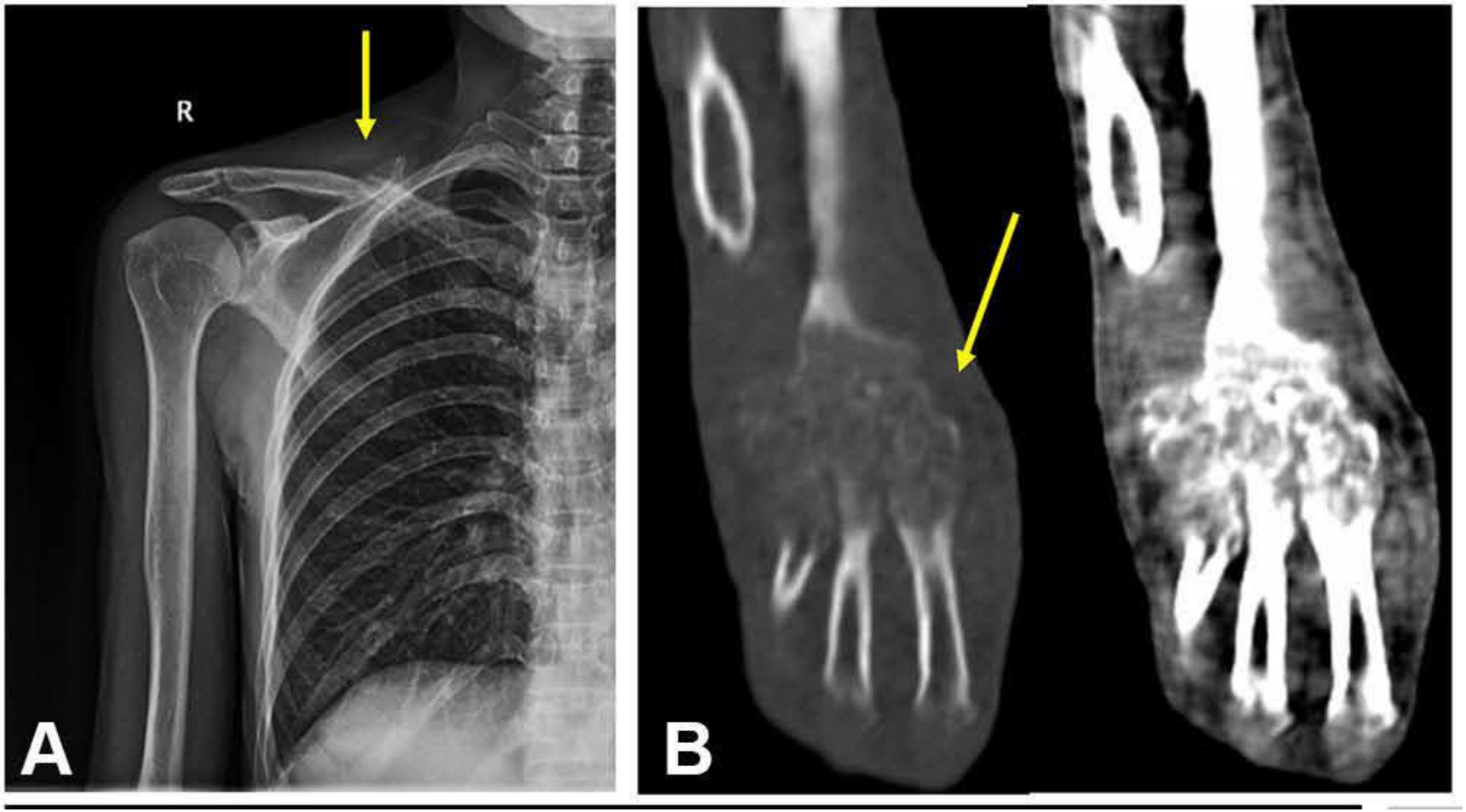
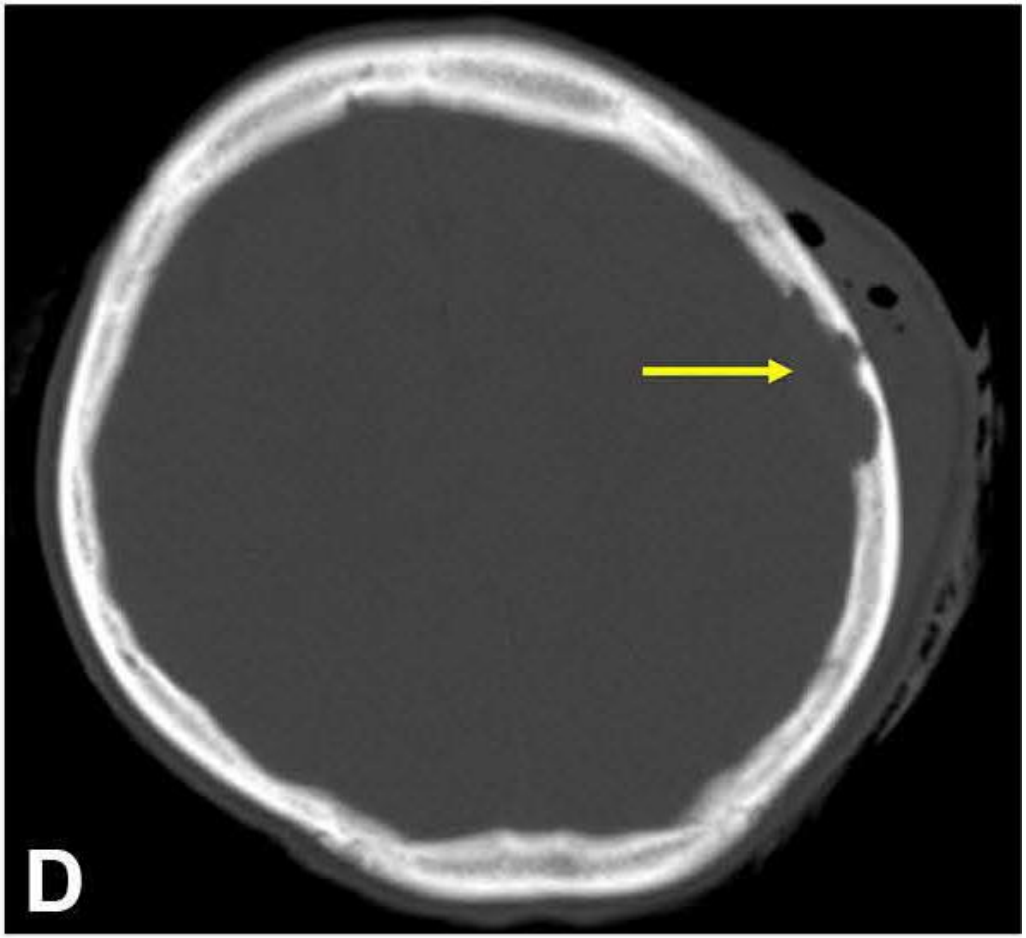


Colonna e cranio



DISSEMINATED DISEASE

- Disseminated disease due to NTM predominantly occurs in patients with advanced HIV infection or other severe immune suppression.
- Although incidence in these patients has declined since the introduction of HAART, disseminated NTM disease is still observed in patients with HIV that have CD4 counts of <50 cells/mm3.
- Generally, MAC causes disseminated disease during HIV.

DISSEMINATED DISEASE

- Disseminated disease also has been reported in patients with immunosuppressive treatment and in stem cell and solid organ transplantation recipients.
- Anti-tumor necrosis factor use is associated with increased risk of NTM disease;
- Several other anti-rheumatic drugs such as high-dose oral corticosteroids, leflunomide, hydroxychloroquine, and drugs classed as highly immunosuppressive, are also associated with NTM disease

…E ANCHE SE ABBIAMO PARLATO SOLO DI FORME EXTRAPOLMONARI VI RICORDO L'IMPORTANZA DELL' OSSERVATORIO IRENE

IRENE

THE ITALIAN REGISTRY OF PULMONARY NON-TUBERCULOUS MYCOBACTERIA

CONTATTI

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E anche se abbiamo parlato solo di NTM…

- … vi ricordo di iscrivervi e seguire le iniziative di STOP TB Italia.

www.stoptb.it