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NTM-TB INSIGHTS

September 2015

Reducing Exposure to Nontuberculous Mycobacteria

Introduction to the Nontuberculous Mycobacteria (NTM)

NTM are bacteria with a lipid-rich, impermeable outer membrane that results in slow growth, antibiotic-resistance, disinfectant-resistance (e.g., chlorine), acid-tolerance, and propensity to stick to pipe surfaces. The lipid-rich outer membrane is the major determinant of their ecology as: (1) NTM grow slowly because they use a great deal of energy to make the long chain fatty acids in the outer membrane, (2) NTM are impermeable to nutrients, but impermeability makes them resistant to disinfectants and antibiotics, (3) NTM are hydrophobic so they are very poor at taking up nutrients, but hydrophobicity drives surface attachment and growth (biofilm formation), where they will not be washed away in pipes, and (4) NTM hydrophobicity means they are more readily aerosolized than other bacteria (1).

Sources of NTM

NTM are normal inhabitants of soils, natural waters, drinking water distribution systems, and household and building plumbing. Highest numbers of NTM are found in recirculating hot water systems in hospitals, apartments, and condominiums. NTM isolates in household plumbing and showerheads have been shown to be identical by DNA fingerprint to NTM from patients (2,3). NTM can survive and grow in phagocytic protozoa and amoebae that normally grow and digest other bacteria; this selection may be why they can grow in human white cells. High numbers of NTM are found in coastal estuaries (Chesapeake and Delaware Bays) and swamps (from Virginia to Texas coast), pine forest soils (Finland, New England), sphagnum vegetation (peat bogs, New England), and cranberry glades (West Virginia, New England). NTM grow in fresh and brackish [sodium chloride (NaCl) = 1-2 %] water, but are absent in ocean water (3% NaCl). Commercial potting soils have high NTM numbers (one million per gram) due to the inclusion of peat, and samples of patients' potting soils yielded NTM that were identical by DNA fingerprint to the NTM isolated from their lungs (4).

How Do NTM End Up in Household Water?

NTM enter drinking water systems attached to soil particulates from surface waters. The source of NTM in household plumbing is piped water from a utility; well-water (groundwater) has very low numbers of NTM. Drinking water distribution systems are ideal habitats for NTM as chlorine kills off competitors for the limited nutrients allowing the slow-growing NTM to grow on low concentrations of nutrients (5). NTM also attach to pipe surfaces where they grow to form biofilms and can't be washed away. Household plumbing is another ideal habitat for NTM: organic matter is present (especially in hot water heaters); NTM are relatively heat resistant, adhere to pipe surfaces and form biofilm, and stagnant times are not bothersome as NTM can grow at low oxygen content. Recirculating hot water systems, such as found in apartments, condominiums and hospitals have very high numbers of NTM as the warmed water supports higher rates of growth. NTM in plumbing are readily aerosolized from taps, showerheads, and humidifiers where they can be inhaled. Humidifiers filled with household water generate a high number of NTM in aerosols (mist). NTM infection can be a consequence of inhalation of an NTM aerosol (shower) or swallowing water with NTM and the NTM aspirated as a consequence of gastric reflux.

NTM Infection Routes

All NTM-infected patients likely have a pre-disposing factor that makes them much more sensitive to NTM. NTM-infected patients are often infected with more than a single NTM strain. The predisposition to NTM infection will never

disappear, thus an NTM patient can possibly be subject to repeated infection. An NTM patient can relapse and the identical strain isolated, or the patient can be infected with a second NTM species or type (6).

How Can We Reduce NTM Exposure?

Studies of NTM sources and the factors that direct their presence in the human environment suggest some measures to reduce exposure. First, if you are worried about swallowing NTM, boil water for 10 min. That will kill NTM. What follows is a list of suggested measures that patients can introduce that may reduce NTM exposure. Few have been rigorously tested and all are based on observations of NTM. Therefore, all of these interventions are experiments.

- **Raise hot water heater temperatures.** Turn up your water heater to 130° F (55° C). NTM patient household plumbing that did not have NTM had higher hot water temperatures (130° F or 55° C or higher), compared to households whose hot water heater temperature was 125° F (50° C) or lower. Recent studies (09/01/15) have shown that raising hot water heater temperatures in 10 homes that had *M. avium* resulted in disappearance of *M. avium* from 9 of the 10 homes by 6 weeks. The study is continuing with more homes.

- ***Install filters that remove bacteria.*** Water filters with pore sizes less than 0.2 micrometers will prevent the passage of NTM. A number of manufacturers produce and sell such filters, primarily for the hospital market. We tested those and showed they prevent passage of NTM. One drawback is that the filters clog up readily, prevent passage for only 30 days, and are expensive.

- ***Drain and refill the hot water heater periodically.*** Hot water heaters have a resident population of NTM. Highest numbers are in the sediment that collects in the bottom. Attach a hose to the drain and let the water, sediment, and bacteria nourish the garden every 6 months.

- ***Disinfect showerheads.*** Showerheads support a rich and diverse microbial population. In one survey 70% of showerheads in the United States had NTM. Unscrew the showerhead and submerge it in undiluted bleach for 30 min. Remove it from the bleach and rinse before screwing it back on the shower tap.

- **Replace showerhead with one that produces streams and not a fine mist.** NTM cells are concentrated in aerosol droplets. Many "low-flow" showerheads produce a fine mist that contains droplets with high numbers of NTM small enough to enter the alveoli. Replace such a "low flow" or misting showerhead with one that has large holes (greater than 1 mm diameter).

- ***Beware of granular activated carbon (GAC) water filters.*** GAC filters are widely marketed and sold directly to consumers to reduce the bad taste of drinking water. GAC binds chlorine and other disinfectants, metals, and organics that impart a bad taste to water. However, they promote the growth of NTM without preventing their passage. The pores of GAC filters are not small enough to prevent bacterial passage; the tortuous path of movement merely delays passage for a while. NTM are quite happy in GAC filters; they attach and grow on the carbon-bound organics and metals as they are resistant to the disinfectant. The manufacturer's recommendation for replacement of the filters is based on the capacity to remove disinfectants, metals, and organics, not on preventing passage of bacteria. In our hands, the recommended time to replace a GAC filter is longer than the time when high NTM numbers pass the filter.

- ***Don't drink from built in refrigerator tap or use ice.*** High numbers of NTM are in refrigerator tap water and ice. In one instance, the DNA fingerprint of the isolates from the refrigerator tap water were identical to those of a patient who drank the water. The tap water coming into the refrigerator collects in a large reservoir and the warmth of the machinery warms the water (before cooling), so the reservoir has lots of NTM.

- ***Get rid of any and all humidifiers.*** Humidifiers generate aerosols with high numbers of NTM, even from reservoir water containing relatively low numbers of NTM (500 colony forming units (CFU)/mL). The new style humidifiers ("ultrasonic") generate a higher density aerosol (visible as a thick fog coming out of the machine) and thus are better than previous humidifiers at transferring water to air, and unfortunately NTM.

- ***Turn off the humidifier attached to the heating/cooling system.*** In an on-going study of NTM-patients in Philadelphia, PA (the same hospital and area where the elderly, slender women were first identified at risk for NTM pulmonary disease), our colleagues at the Lankenau Medical Research Institute (led by Dr. Leah Lande) discovered that all the NTM-infected women with humidifiers have those that feature simple fabric filters with a channel above with holes for tap water (NTM) to drip through (like "swamp coolers" in the desert southwest). I think the NTM attach to the filter material (maybe grow) and are transferred via the household air that is drawn through the filter. Humidity helps breathing, but it exposes one to NTM-laden aerosols.

- ***Avoid dusts from potting soil.*** Commercial potting soil is rich in peat and peat harbors very high numbers of NTM (1 million per gram). As peat or potting soil dries, the dust generated has high numbers of NTM. In a study of pulmonary NTM patients, we found that a proportion (who were gardeners) had been infected from their potting soil.

- **Ultraviolet (UV) Light Disinfection.** There are a number of companies manufacturing and selling whole house or single tap devices to kill microorganisms in drinking water with UV light. However, 5-fold higher dosage is needed to kill 99.9 % of NTM cells than to kill *Escherichia coli*, the standard. If a UV system can provide at least a 5-fold higher dosage (the combination of UV light strength and duration of exposure), it will kill NTM.

Pink Slime and NTM

Recently, we discovered that whenever a biofilm sample has pink-pigmented bacteria (*Methylobacterium*), there are no NTM. Evidently, the two cannot coexist in biofilms. Taps or showerheads in a home with NTM don't have *Methylobacterium*. As not all taps or showerheads in a home will have NTM, use those that show evidence of a pink scum or film; the pink scum will be seen on shower curtains, shower walls, or in crevasses in a shower or sink.

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References:

1. Brennan, P.J. and H. Nikaido. 1995. The envelope of mycobacteria. Annu. Rev. Microbiol. 64: 29-63.
2. Falkinham, J. O. III, M. D. Iseman, P. de Haas, and D. van Soolingen. 2008. *Mycobacterium avium* in a shower linked to pulmonary disease. J. Water Health. 6: 209-213.
3. Falkinham, J.O., III. 2011. Nontuberculous mycobacteria from household plumbing of patients with nontuberculous mycobacteria disease. Emerg. Infect. Dis. 17: 419-424.
4. De Groot, M. A., N. R. Pace, K. Fulton, and J. O. Falkinham, III. 2006. Relationships between *Mycobacterium* isolates from patients with pulmonary mycobacterial infection and potting soils. Appl. Environ. Microbiol. 72:7062-7606.
5. Falkinham, J.O., III, C.D. Norton, and M.W. LeChevallier. 2001. Factors influencing numbers of *Mycobacterium avium*, *Mycobacterium intracellulare*, and other mycobacteria in drinking water distribution systems. Appl. Environ. Microbiol. 67:1225-1231.
6. Wallace, R.J. Jr., Y. Zhang, B.A. Brown-Elliott, M.A. Yakrus, R.W. Wilson, L. Mann, L. Couch, W.M. Girard, and D.E. Griffith. 2002. Repeat positive cultures in *Mycobacterium intracellulare* lung disease after macrolide therapy represent new infections in patients with nodular bronchiectasis. J. Infect. Dis. 186: 226-273.

Treatment Recommendations for Slowly Growing Nontuberculous Mycobacterial Infections

Nontuberculous mycobacteria, both slow growing (SGNTM) and rapidly growing mycobacteria (RGNTM), are normal inhabitants of the environment. Evidence is mounting that concentrations of NTM are highest in potable water sources, and that NTM are then consumed or inhaled by humans particularly in household plumbing. Once the NTM are introduced into these environments, they readily incorporate themselves into a biofilm within plumbing and plumbing fixtures, becoming then a source for infection to a vulnerable host when ingested or aerosolized (1,2). In addition to causing significant pulmonary disease, SGNTM have been implicated in numerous extrapulmonary infections such as dissemination in severely immunocompromised patients; bone and joint infections related to injections with SGNTM-contaminated medications; and skin and soft tissue infections related to wound contamination with SGNTM pathogens.

The most common SGNTM species encountered in clinical practice is the *Mycobacterium avium* complex (MAC). The species in MAC include *M. intracellulare, M. avium*, and *M. chimaera*. Other SGNTM species that are commonly encountered in clinical practice include *M. kansasii, M. haemophilum*, and *M. marinum*. Other less commonly encountered SGNTM pathogens include *M. xenopi* (which is less common in the USA, but a major pathogen in pulmonary disease in Canada, Northern Europe and other parts of the world), *M. simiae* (more common in the desert southwest of the USA), *M. szulgai, M. scrofulaceum, M. malmoense,* and the *M. terrae* complex. It is imperative that the laboratory identifies the mycobacteria to the species level to provide the clinician the best information that will help guide treatment options.

Clinical presentations with pulmonary SGNTM infections present in two broad categories. The first involves upper lobe fibrocavitary lesions that resemble pulmonary tuberculosis and most often is associated with prior tobacco use. The second presentation is one of nodular disease which may be diffuse or focal. The nodular disease may or may not be associated with bronchiectasis. This presentation has historically been described in MAC disease although all other SGNTM have shown this same radiographic distribution (3). The phenotype known as “Lady Windermere Syndrome” which described a tall, slender, female with pectus excavatum, mitral valve prolapse, and right middle lobe and lingular disease is perhaps the most common description for focal nodular, bronchiectatatic SGNTM presentation (4,5). Recently, new associations with diffuse nodular presentation have been well characterized in patients with cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations (6,7).

A new area of focus for study regarding the route of acquisition for NTM and other pathogens has been to study mechanisms of gastroesophageal reflux (GERD) as well laryngopharyngeal reflux (LPR) disease. Most studies to date have dealt with how GERD or LPR are best diagnosed, with virtually no studies on the microbiology of GERD and LPR, nor focusing on nonmedical treatment of GERD and LPR (8,9,10). The concept of acquisition of NTM into the respiratory tract via silent reflux and aspiration is certainly intriguing and in need of further study. More often than not, clinicians are very quick to offer proton pump inhibitors (PPIs) to patients as treatment for reflux, heartburn, cough and asthma. While PPIs may lessen reflux-associated symptoms, this does not prevent or solve the mechanical dysfunction of GERD or LPR; in fact, many studies have now demonstrated that the use of PPIs increase a patient’s chance for community acquired pneumonia (11). Although NTM are not currently associated with the definition of community acquired pneumonia, acquisition of this group of organisms must be considered as a potential route of acquisition of all NTM species. Treatment of GERD/LPR (which may lead to airway colonization or infection) is multimodal but should include sleeping with hips to shoulders elevated between 30-45 degrees; limiting hourly liquids if patient has a hiatal hernia or known GERD; limiting liquids later in the evening; avoiding evening consumption of substances that can promote GERD

through a variety of mechanisms such as alcohol, carbonated beverages, caffeine, fatty foods and tomato products, to name just a few.

Airway hygiene is also essential to incorporate in the multimodal approach to treatment of pulmonary disease with SGNTM. Since most of these infections are associated with bronchiectasis and /or airway contamination with gastric contents, attention to mechanical airway hygiene is necessary. Use of any device such as a handheld vibratory device or a mechanical vest product, with or without the use of nebulized hypertonic saline, may prove exceedingly beneficial for clearance of mucus inflammatory debris.

Lastly, antibiotic treatment for SGNTM involves the use of preferably 3 to 4 antibiotics. The 3 most common antibiotics used are rifampin/rifabutin, ethambutol, and azithromycin/clarithromycin. The 2007 ATS/IDSA guidelines state that for nodular disease the clinician can use these 3 classes of antibiotics together on a thrice weekly basis, but if there is a substantial burden of disease or cavitary disease, one should use them on a daily basis (12,13). It is important to remember that there are significant drug-drug interactions if using clarithromycin and rifabutin together. The clarithromycin will slow the metabolism of rifabutin leading to accumulation of rifabutin and frequently leading to joint aches, fever, fatigue, liver function abnormalities, and transient skin color changes. If azithromycin is used with rifabutin, this reaction will not be encountered. If a patient has a significant burden of disease or cavitary disease, the addition of an aminoglycoside is warranted. Dosing of the aminoglycoside should be 12-15mg/kg on a THRICE WEEKLY basis and the patient must be monitored closely for signs of neuro/nephrotoxicity. Generally, use of aminoglycoside is limited to a duration of 2-6 months because of toxicity. The goal for treatment duration for all SGNTM is to have 12 months of negative cultures on therapy. Most importantly, NEVER USE A MACROLIDE AS MONOTHERAPY for treatment of SGNTM infections as macrolide resistance will rapidly develop and render the macrolide useless as an effective antibiotic for treatment of these infections (13,14).

Treatment for SGNTM pulmonary infections requires a multimodal approach from the clinician. Attention to minimizing acquisition of the organism through education about GERD/LPR, providing the patient with appropriate airway clearance devices, as well as adequate antibiotic treatment are imperative to success.

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References:

1. Falkinham JO, 3rd, Iseman MD, de Haas P, van Soolingen D. *Mycobacterium avium* in a shower linked to pulmonary disease. J Water Health. 2008;6(2):209-13.
2. Mullis SN, Falkinham JO, 3rd. Adherence and biofilm formation of *Mycobacterium avium, Mycobacterium intracellulare* and *Mycobacterium abscessus* to household plumbing materials. J Appl Microbiol. 2013;115(3):908-14.
3. Griffith DE, Aksamit TR. Bronchiectasis and nontuberculous mycobacterial disease. Clin Chest Med. 2012;33(2):283-95.
4. Reich JM, Johnson RE. *Mycobacterium avium* complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The Lady Windermere syndrome. Chest. 1992;101(6):1605-9.
5. Kartalija M, Ovrutsky AR, Bryan CL, Pott GB, Fantuzzi G, Thomas J, et al. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. Am J Respir Crit Care Med. 2013;187(2):197-205.
6. Bienvenu T, Sermet-Gaudelus I, Burgel PR, Hubert D, Crestani B, Bassinet L, et al. Cystic fibrosis transmembrane conductance regulator channel dysfunction in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2010;181(10):1078-84.
7. Prevots DR, Adjemian J, Fernandez AG, Knowles MR, Olivier KN. Environmental risks for nontuberculous mycobacteria. Individual exposures and climatic factors in the cystic fibrosis population. Ann Am Thorac Soc. 2014;11(7):1032-8.
8. Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, et al. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol. 2015;21(12):3619-27.

9. Scott DR, Simon RA. Supraesophageal Reflux: Correlation of Position and Occurrence of Acid Reflux-Effect of Head-of-Bed Elevation on Supine Reflux. J Allergy Clin Immunol Pract. 2015;3(3):356-61.
10. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet. 1999;354(9193):1851-8.
11. Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One. 2015;10(6):e0128004.
12. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416.
13. Philley JV, Griffith DE. Treatment of slowly growing mycobacteria. Clin Chest Med. 2015;36(1):79-90.
14. Nash KA, Inderlied CB. Genetic basis of macrolide resistance in *Mycobacterium avium* isolated from patients with disseminated disease. Antimicrob Agents Chemother. 1995;39(12):2625-30.

50 Years Ago – Aspects of Bacterial Resistance in Tuberculosis

The J. Burns Amberson Lecture presented by George Canetti at the American Thoracic Society Conference in 1965 (*Am Rev Respir Dis*. 1965. 92:687-703) – Part 4 of 5.

The reason I have chosen bacterial resistance in tuberculosis as the subject for this lecture is not merely because I have done some work in the field, but because it is my strong belief that a revival of active interest in resistance is needed. The neglect into which this most promising field of research has fallen is amazing. Bacterial resistance is as old as antituberculosis chemotherapy.

III. Differences in Resistance Type - Distributions between Acquired Resistance and Primary Resistance

So much has been written recently on primary resistance that I shall restrict myself to one point. What I have in mind has been observed at the French Centre for Primary Resistance, and may be of some biologic importance. In France, the figures for primary resistance are relatively high, compared with those of other western countries. Among 2,144 untreated patients with pulmonary tuberculosis whose strains were collected in 1963 and 1964 from different parts of the country (although not on a strictly sampling basis), the overall incidence of a primary resistance to at least one of the three usual drugs was 9.8%. Resistance to one drug was found in 6.4% of the patients; to two drugs, in 2.4%; and to three drugs, in 1.1%. Resistance to streptomycin occurred in 7.6% of the patients; to isoniazid, in 4.6%; and to PAS, in 2.2% (44). This situation, disquieting as it is, provided the opportunity to study unusual numbers of primarily resistant strains. For isoniazid, the number of such strains was 98. *The level of isoniazid resistance was considerably lower than the level found for strains with acquired resistance.* This is the point which deserves attention.

The figures are given in table 3. The material from which the data on the level of *acquired* resistance are drawn are 443 drug-treated resection cases with strains that were isolated and tested between 1957 and 1963 (5a). The method applied was, in both cases, the proportion method with its criteria, and all the tests were supervised by the same bacteriologists. In both groups, the comparison concerns all the strains classified as isoniazid resistant according to the adopted criterion. The *levels* of resistance were compared by assessing the maximal drug concentration, among those employed, to which the strains were *homogeneously* resistant.

The difference between strains with primary resistance and strains with acquired resistance proved considerable. A level of homogeneous resistance to isoniazid not exceeding 0.2 γ per milliliter was shown by as much as 50% of the strains with primary resistance in contrast to the 26% of the strains with acquired resistance; and a level reaching 10 γ per milliliter or more was shown by only 11% of the former versus 53% of the latter. Nothing of the sort appeared in

streptomycin resistance. A comparison based on the same principles disclosed approximately the same levels for both strains; if anything, the levels for primary resistance were slightly higher (table 3, see original publication).

It may be questioned whether a comparison between strains with acquired resistance *isolated and tested from 1957 to 1963*, on the one hand, and primarily resistant strains *isolated and tested in 1963 and 1964*, on the other, is acceptable. Actually, such a wide time range for the resistant strains *considered at their source* is not only acceptable, but desirable, as tuberculosis originates often in infection acquired several years earlier. The choice of these two different time periods was a deliberate one. It may be questioned further whether using resected specimens for assessing the average level of acquired resistance does not introduce a distortion, as resection material is usually derived in a large proportion from patients with *very long* isoniazid treatment, and hence, may show very high levels of isoniazid resistance. By contrast, the source of primary resistance often may have been patients who had less protracted treatment. Although this objection is undoubtedly valid, taking it into account does not significantly change the problem, as acquired isoniazid resistance attains a high level *early.* In the resection cases in which isoniazid had been given for only 6 to 12 months, the proportion of strains homogeneously resistant to at least 10 γ per milliliter was 43% versus 56% in the patients who received isoniazid for more than a year; the corresponding figure for primary resistance, as stated above, was 11%. The difference in the levels remains obvious.

The reasons for the lower levels in primary isoniazid resistance may be twofold. The resistance may have *dropped* in the newly infected host through prolonged multiplication of the resistant strain in the absence of isoniazid. In studies *in vitro*, although most strains remain at an unaltered level of resistance after numerous passages in media without isoniazid, some strains show a more or less considerable fall. The other factor at work may be the well-known higher experimental *virulence* of the low isoniazid-resistant, catalase-positive strains, compared with the virulence of the high-resistant, catalase-negative ones (45). As a consequence, the proportion of the contaminations resulting eventually in tuberculosis disease may be greater with the former than with the latter. The strains demonstrated in primary resistance would then represent, to a certain extent, only a *selection among all the isoniazid-resistant strains available for transmission*, a selection operated by the persons exposed. Although hypothetical, it is possible that both of these mechanisms may be relevant. The first mechanism stresses the importance of studies *in vivo*, as well as *in vitro*, on the stability of isoniazid resistance, such as those of Schmidt and associates (46) and those of Good (47). The second mechanism lends some support to the opinion frequently expressed that the reduced *experimental* virulence of catalase-negative strains must have its counterpart in *human* tuberculosis. The counterpart is certainly limited, since undisputable cases of cavitary tuberculosis produced by highly isoniazid-resistant, catalase-negative strains do exist. Nevertheless, there would now be some evidence of a lesser "over-all noxiousness" of this type of resistant strain for man. The problem has obviously important epidemiologic implications.

The differences observed in isoniazid-resistant strains, according to whether resistance is primary or acquired, may shed some light on a hitherto unsatisfactorily explained phenomenon: the lasting predominance of primary *streptomycin* resistance, in many countries. In the United States (48, 49), in Great Britain (50), as well as in France (44,51), primary resistance to streptomycin remains either notably more frequent than, or almost as frequent as, primary resistance to isoniazid. In the recent French statistics (44), resistance to streptomycin *alone* existed in 95 of a total 163 patients with resistance to streptomycin and of 211 patients with any type of primary resistance. On the other hand, new cases of *acquired* resistance to streptomycin *alone* have been rare for many years – a situation due to the therapeutic predominance of isoniazid. In the resection material chosen for the comparison of streptomycin resistance levels in primary and in acquired resistance (table 3, see original publication), in only 7 cases among more than 400 was there resistance to streptomycin *alone*, an almost negligible figure.

This discrepancy between the frequency of resistance to streptomycin alone in *primary* resistance and its present rarity in *acquired* resistance calls for an obvious interpretation. The infection, in most cases of primary resistance to streptomycin alone, must have come from patients treated in the early days of chemotherapy by streptomycin alone. The transmission of the streptomycin-resistant strain could have occurred either at that time, or later, through relapse of the disease in an apparently cured patient harboring such a strain. This interpretation probably applies to many cases and may explain why the relative prevalence of *primary streptomycin* resistance, compared with the prevalence of primary isoniazid resistance, is lower in places where antituberculosis chemotherapy was not in widespread use at the time of treatment with streptomycin alone (52,53).

However, this may not be the whole story. In view of the lasting frequency of these cases, and in view of the fact that they occur even in very young patients whose infection is unlikely to date so far back (among 22 cases of primary resistance in patients aged less than 20 years, 8 showed a strain resistant to streptomycin alone (44)), the question arises whether the phenomenon is not linked to the trends of primary *isoniazid* resistance. Both mechanisms discussed above may be involved. On the one hand, it may well be that some of the strains that showed up as resistant to streptomycin *alone* in primary resistance were resistant to *streptomycin and isoniazid* at the time of transmission, but have lost their resistance to isoniazid in the new host. Nothing fundamental opposes such a hypothesis, which is in accordance with the greater stability of streptomycin-resistance levels at passages *in vitro*. On the other hand, if *some* of the strains with acquired resistance to isoniazid are incapable (through insufficient virulence) of producing new cases of tuberculosis except in rare circumstances, the *relative* frequency of isoniazid resistance, in comparison with the frequency of streptomycin resistance, must necessarily be lower in primary resistance than in acquired resistance. For no such eliminating factor exists for streptomycin-resistant strains: they are known to be fully virulent: whatever the level of resistance. Although nothing definitive can be said at present on this problem, some influence of these two factors on the lasting high frequency of primary resistance to streptomycin is most likely. With growing remoteness of the period when a purely streptomycin-resistant, bacillary reservoir could have been built up in the population through the type of chemotherapy used, watching for future trends in this field will be especially rewarding.

Primary resistance, then, is not a mere *replication* of acquired resistance. The differences between them, as observed at a given moment, disclose more than the changes which have occurred in chemotherapy, and the long delay necessary for their consequences to appear in so slowly spreading a disease as tuberculosis. Other factors, such as altered virulence of the resistant strains, or instability inherent to certain types of resistance, may also be at work in producing the differences. By telling the *long-term* story of the resistant strains resulting from the totality of internal and external factors involved, primary resistance carries information of great moment.

References – see original publication

Recent Staff Publications

Nichols DP, Chmiel JF. Inflammation and its genesis in cystic fibrosis. Pediatr Pulmonol. **2015 Oct**;50 Suppl 40:S39-56. doi: 10.1002/ppul.23242.

Bennett DT, Zamora M, Reece TB, Mitchell JD, Cleveland JC Jr, Grover FL, Babu AN, Meguid RA, Fullerton DA, Weyant MJ: Continued Utility of Single-Lung Transplantation in Select Populations: Chronic Obstructive Pulmonary Disease. Ann Thorac Surg. **2015 Aug**;100(2):437-42.

Koh WJ, Jeong BH, Jeon K, Park HY, Kim SY, Huh HJ, Ki CS, Lee NY, Shin SJ, Daley CL: Response to Switch from Intermittent Therapy to Daily Therapy for Refractory Nodular Bronchiectatic *Mycobacterium avium* Complex Lung Disease. Antimicrob Agents Chemother. **2015 Aug;**59(8):4994-6.

Walter ND, Dolganov GM, Garcia BJ, Worodria W, Andama A, Musisi E, Ayakaka I, Van TT, Voskuil MI, de Jong BC, Davidson RM, Fingerlin TE, Kechris K, Palmer C, Nahid P, Daley CL, Geraci M, Huang L, Cattamanchi A, Strong M, Schoolnik GK, Davis JL: Transcriptional Adaptation of Drug-tolerant *Mycobacterium tuberculosis* During Treatment of Human Tuberculosis. J Infect Dis. **Sep 15;**212(6):990-8.

Salfinger M, Migliori GB: Bedaquiline: finding the pores on the pot. Eur Respir J. **2015 Jul**;46(1):289-91.

Bai X, Dinarello CA, Chan ED: The role of interleukin-32 against tuberculosis. Cytokine. 2015 Jul 2. pii: S1043-4666(15)30002-8. doi: 10.1016/j.cyto.2015.06.013. [Epub ahead of print]

Hasan NA, Davidson RM, de Moura VC, Garcia BJ, Reynolds PR, Epperson LE, Farias-Hesson E, DeGroote MA, Jackson M, Strong M: Draft Genome Sequence of *Mycobacterium chelonae* Type Strain ATCC 35752. Genome Announc. **2015 May** 28;3(3).

Sagel SD, Thompson V, Chmiel JF, Montgomery GS, Nasr SZ, Perkett E, Saavedra MT, Slovis B, Anthony MM, Emmett P, Heltshe SL: Effect of treatment of cystic fibrosis pulmonary exacerbations on systemic inflammation. Ann Am Thorac Soc. **2015 May**;12(5):708-17.

Mauchley DC, Mitchell JD. Current estimate of costs of lung cancer screening in the United States. Thorac Surg Clin. **2015 May**;25(2):205-15.

Bishwakarma R, Kinney WH, Honda JR, Mya J, Strand MJ, Gangavelli A, Bai X, Ordway DJ, Iseman MD, Chan ED: Epidemiologic link between tuberculosis and cigarette/biomass smoke exposure: Limitations despite the vast literature. Respirology. **2015 May**;20(4):556-68.

Honda JR, Hess T, Malcolm KC, Ovrutsky AR, Bai X, Irani VR, Dobos KM, Chan ED, Flores SC: Pathogenic nontuberculous mycobacteria resist and inactivate cathelicidin: implication of a novel role for polar mycobacterial lipids. PLoS One. **2015 May** 18;10(5):e0126994. doi: 10.1371/journal.pone.0126994. eCollection 2015.

Winthrop KL, Ku JH, Marras TK, Griffith DE, Daley CL, Olivier KN, Aksamit TR, Varley CD, Mackey K, Prevots DR: The tolerability of linezolid in the treatment of nontuberculous mycobacterial disease. Eur Respir J. **2015 Apr**;45(4):1177-9.

Bai X, Shang S, Henao-Tamayo M, Basaraba RJ, Ovrutsky AR, Matsuda JL, Takeda K, Chan MM, Dakhama A, Kinney WH, Trostel J, Bai A, Honda JR, Achcar R, Hartney J, Joosten LA, Kim SH, Orme I, Dinarello CA, Ordway DJ, Chan ED: Human IL-32 expression protects mice against a hypervirulent strain of *Mycobacterium tuberculosis*. Proc Natl Acad Sci U S A. **2015 Apr** 21;112(16):5111-6.

Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, Nachman S, Oliveira R, Moro RN, Shang N, Goldberg SV, Sterling TR; International Maternal Pediatric and Adolescents AIDS Clinical Trials Group; Tuberculosis Trials Consortium: Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. **2015 Mar**;169(3):247-55.

Huitt GA, Daley CL: Nontuberculous mycobacteria. Clin Chest Med. **2015 Mar**;36(1):xi-xii.

Honda JR, Knight V, Chan ED: Pathogenesis and risk factors for nontuberculous mycobacterial lung disease. Clin Chest Med. **2015 Mar**;36(1):1-11.

Kasperbauer SH, De Groote MA: The treatment of rapidly growing mycobacterial infections. Clin Chest Med. **2015 Mar**;36(1):67-78.

Martiniano SL, Nick JA: Nontuberculous mycobacterial infections in cystic fibrosis. Clin Chest Med. **2015 Mar**;36(1):101-15.

Mitchell JD: Surgical approach to pulmonary nontuberculous mycobacterial infections. Clin Chest Med. **2015 Mar**;36(1):117-22.

Meetings

- **FDA Public Meeting for NTM Patients, Caretakers and Advocates**
  Patients with nontuberculous mycobacterial lung infections are invited to a public meeting with the FDA, taking place 9 a.m. to 5 p.m. Oct. 15, 2015 at the FDA White Oak Campus (Building 31, Great Room) in Silver Spring, Maryland. The morning session will be a facilitated patient discussion, followed by a scientific discussion in the afternoon. Participants also have the option to watch the live meeting webcast and comment online. RSVP by Oct. 7
- **The 52nd Semi-Annual Denver TB Course**, October 14-17, 2015; Molly Blank Conference Center at National Jewish Health Main Campus. Click here for more information and registration.
- **46th Union World Conference on Lung Health – A New Agenda: Lung Health Beyond 2015**, December 2-6, 2015, Cape Town, South Africa
- **20th Annual Conference of the International Union Against Tuberculosis and Lung Disease – North American Region**, February 24-27, 2016. Sheraton Denver Downtown Hotel, Denver, CO
- **National Tuberculosis Controllers Association Meeting**, February 24-27, 2016, Sheraton Denver Downtown Hotel, Denver, CO
- **Tuberculosis Co-Morbidities and Immunopathogenesis**, February 28-March 3, 2016, Keystone Resort, Keystone, CO
- **The 53rd Semi-Annual Denver TB Course**, April 6-9, 2016; Molly Blank Conference Center at National Jewish Health Main Campus. Click here for more information and registration.
- **Front Range Mycobacteriology**, June 7-10, 2016, Colorado State University, Fort Collins, CO

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