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Content

- Have we fixed the problem?
- Subclinical infections
- Limitations of IGRT
- BIPAD
- Specific pathogens
- Conclusions















Risk factors for pneumonia in CVID

• Low IgA

- Low IgG trough on replacement
- Chronic sinusitis
- Bronchiectasis
- Low CSMB



(Quinti I. et al. J Clin Immunol. 2011)

Subclinical Infection







Respiratory Infections and Antibiotic Usage in Common Variable Immunodeficiency

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- 69 CVID patients
- 54 viral swabs
- 43 sputum samples (combined mean 1.4 samples/patient)
- Diary data for 6210 days or 90 days per patient
- 170 exacerbations with antibiotics used in 76 with a delay of 5days
- Purulent sputum responded more quickly to antibiotics than sore throat or upper respiratory tract symptoms
- 56% found a potentially pathogenic virus and 33% a bacterium





J Clin Immunol. 2017 February ; 37(2): 153-165. doi:10.1007/s10875-016-0367-1

Increased Incidence of Fatigue in Patients with Primary Immunodeficiency Disorders: Prevalence and Associations Within the US Immunodeficiency Network Registry

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- Self reported fatigue has the greatest impact on QoL and is associated with poorer survival and worse outcomes in other diseases
- USIDNET data 2537 patients 18% with PID have fatigue
- Fatigue in the general population is reported at 6-7.5%
- Fatigue is present in 24.9% of PAD vs 6.4% non PAD
- CVID 30% reported fatigue the highest levels
- Association with depression, bronchiectasis and arthritis (also Low T cells, leukopenia, granuloma, colitis, adrenal insufficiency, IBD, interstitial lung disease, hepatomegaly, eosinophilic esophagitis, and coeliac disease)
- No difference in fatigue between IVIg and SCIg
- Psychology, non-infectious, infectious?

PAD and Fatigue

Shortcomings of current IGRT

- Does not contain IgA
- Does not contain IgM
- Quality is determined with titres to measles, diptheria and polio may not be ideally suited for QC for PID indication
- IgG may not reach mucosal sites appropriately
- Ability to manage inflammatory autoimmune aspects

Immunoglobulin testing

- FDA measles, diptheria and polio
- These are in fact not the key pathogens we find in PID patients
- High titre RSV immunoglobulinwas found to also have higher titres to a number of other viruses
- Either individuals were high responders
- Or individuals encountered a higher virus frequency
- Or a combination

Therapeutic immunoglobulin selected for high antibody titer to RSV also contains high antibody titers to other respiratory viruses

Jordan S. Orange^{1*}, Wei Du² and Ann R. Falsey³



lgM

- Removal of apoptotic cells
- B cell homeostasis
- Modulation of inflammation
- Role in eliminating infection
- Autoimmunity and atherosclerosis
- Reduced IgM following B cell ablation therapies



Prophylactic antibiotics

The NEW ENGLAND **Prophylactic Antibiotics** JOURNAL of MEDICINE AUGUST 25, 2011 Azithromycin for Prevention of Exacerbations of COPD Much of the data is from non PID • What are they doing – infection, 0.9 carriage, inflammation, resistance Proportion Free of COPD Exacerbation 0.7 • Significant use of macrolides 0.6 • Role of rotation 0.5 0.4 • Individual response 0.3 Place • 'Good but no cigar' 0.2 <0.001 by log-rank test and Wilcoxon signed-rank test</p> 180 Follow-up (days) **Clinical Commentary Review Antibiotic Prophylaxis in Primary Immune Deficiency** Disorders Merin Kuruvilla, MD, and Maria Teresa de la Morena, MD Dallas, Tex

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Rhinovirus impact

Outgrowth of the Bacterial Airway Microbiome after Rhinovirus Exacerbation of Chronic Obstructive Pulmonary Disease

Philip L. Molyneaux^{1,2}, Patrick Mallia^{1,2,3}, Michael J. Cox^{1,2}, Joseph Footitt^{1,2,3†}, Saffron A. G. Willis-Owen¹, Daniel Homola¹, Maria-Belen Trujillo-Torralbo^{1,2,3}, Sarah Elkin^{1,3}, Onn Min Kon^{1,2,3}, William O. C. Cookson^{1,2}, Miriam F. Moffatt^{1,2*}, and Sebastian L. Johnston^{1,2,3*}

- COPD (14) and healthy controls (17) given rhinovirus and induced sputum pre and d5,15 and 42
- Sputum 16S ribosomal RNA microbiome
- Day 15 6 fold increase in 16S copy number and 16% increase in proteobacterial sequences
- Most notably *Haemophilus influenzae* (p 2.7x10⁻²⁰) from a pre-existing community and only in COPD
- Still present at 42 days
- Rhinovirus predicts secondary bacterial infection

<u>Linked Dis</u> 2014 New 15:210(10):1649-67. doi: 10.1093/india/ju028. Epub 2014 Jun 6. **High nasopharyngeal pneumococcal density, increased by viral coinfection, is associated with invasive pneumococcal pneumonia.** Wolter N¹. Temas S². Cohen C³. Maddi S⁴. Venter M⁴. Mouse J⁶. Walaza S⁶. Malone-Kookong B⁶. Gnome M⁷. do: Plessis M⁴. Maacmani L⁶. Pretorius M⁶. Hiltensone C¹. Sumodi H⁵. Materix S¹. Namana E¹¹. Namana R¹². - on Gotteen A¹.





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