Immunity in Bariatric patients.

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Background:

The bariatric population presents several challenges and very little is known on the immune response of these patients. Bacterial infections and viral infections might induce a different response. As a matter of fact, bariatric patients have shown improved survival following bacterial infections (part of the so called "Bariatric paradox") as well as increased mortality during the influenza pandemic. In general, all bariatric patients have increased risk for sepsis due to type two diabetes mellitus, steroids usage (inhaled for COPD/asthma and intra-venous for other chronic conditions including arthritis), vessels diseases, obstructive sleep apnea, atelectasia (lung infections) and other substances abuse. Co-morbidities such as cancer, hypertension, hypercholesterolemia, renal/liver impairments (NASH), may all have an impact on the pharmacokinetics/pharmacodynamics (PK/PD) of antibiotics. We expect there will be significant number of drug interactions in most of those patients, in particular those undergoing surgery or admitted to the ICU. We will present two studies that are currently conducted in our bariatric centers in Imperial College trust in London looking at bacterial and viral infections in this challenging population.

Objectives:

The evidence shows obesity as an inflammatory state which may contribute to obesity-associated favorable as well as adverse outcomes. Visceral fat is related to the production of adipokines and the difference in the immune response in this population. The bariatric population presents challenges due to co-morbidities but nevertheless it shows better outcome for heart ischemia, bacterial infections such as community acquired pneumonia. This has been called the "Bariatric paradox". On the contrary, the last influenza pandemic showed that immunity against virus infections is different compared to bacteria and in fact mortality was higher in high (body mass index (BMI) $\geq$ 35 kg/m^2) BMI individuals compared to the lean population.

The first study we will present is currently looking at the Pharmacokinetics and pharmacodynamics of Amoxicillin-clavulanate, clindamycin/gentamicin, VANcomycin for antimicrobial prophylaxis during Elective laparoscopic bariatric surgery (PAVANE study). There are only limited data describing the pharmacokinetic (PK) and pharmacodynamics (PD) properties of antimicrobials in the obese population. Perioperative antimicrobial prophylaxis should ensure that adequate antibiotic levels are maintained above the minimum inhibitory concentration (MIC) from the time of incision and throughout the procedure in order to prevent surgical site infections (SSIs). The benefits of perioperative antimicrobial prophylaxis in preventing SSIs have been clearly

demonstrated through numerous trials and endorsed in various guidelines [1-3]. The principal aim of the PAVANE study, which is a single center study at SMH will be to better understand the PK/PD of antibiotics used in surgical prophylaxis for elective laparoscopic bariatric patients, to determine the PK profile of antibiotics used and to assess the impact of a single dose on the microbiome.

The second study, which has been recently completed, is aimed at identifying reasons why the immune system in bariatric patients during viral infections such as influenza increase mortality and does not protect this population.

Methods:

Study one (PAVANE):

Numerous microbial species have been implicated as SSIs pathogens. In bariatric surgical procedures, the predominant organisms include Gram-positive bacteria such as staphylococci (in particular, *Staphylococcus aureus*), streptococci and enterococci, Gram-negative pathogens such as enterobacteriaceae (including *Proteus mirabilis*, *Serratia marcescens*, *Enterobacter* and *Escherichia coli*) and anaerobes (in particular, *Bacteroides fragilis*) [1]. Based on this epidemiological data, cefazolin is the most often used agent [2], but other drugs vary among different centers, with a total of 37 different antibiotic regimens found in a recent review [3]. However, little is known about the impact of a single dose of antibiotic on the human microbiome and its role in early post-operative complications [4]. The patients and will be included at Imperial College Healthcare NHS Trust in London in the pre-assessment clinic and they will follow the trust protocol.

Inclusion criteria:

- Age >18 years and <90 years.
- Patients scheduled for elective laparoscopic bariatric surgery at Imperial College Healthcare NHS Trust.
- Prescription of IV co-amoxiclav, clindamycin/gentamicin and vancomycin according to our bariatric protocol for surgical prophylaxis.
- Informed consent by patient or legally authorised representative to participate in study and to store specimens for immediate and future analysis.

Exclusion criteria:

- Age below 16 years.
- No consent.
- Prior prescription of the study antibiotic within the previous 72-hours.
- Known or suspected allergy to the study drugs.

Collection of clinical samples: Patients will require pre-assessment tests (FBC, CRP, renal and liver function tests) as per hospital guidelines and the following additional samples will be collected:

- Blood samples for antibiotic levels at T30 (30 minutes after the end of the IV administration) T60, T120, T240 (generally in recovery or on the ward)
- Rectal swabs (before and after the operation) for analysis of faecal microbiome
- Tracheal aspirate before and after administration of antibiotics (all patients are intubated) for the analysis of the respiratory microbiome
- 20mL urine sample will be collected on the ward post operatively to measure the amount of drug cleared via the renal system

30 patients undergoing elective laparoscopic bariatric surgery will be enrolled for the administration of the standard prophylactic antibiotic dosing regimens as per hospital guidelines and after informed consent. Additional 5 volunteers (3 obese patients but without undergoing surgery and 2 non-obese patients undergoing a laparoscopic procedure such as cholecystectomy) will also be enrolled as controls for administration of antibiotics and monitoring of levels to assess the potential impact of surgery and obesity on the PK/PD.

Second study:

The aim of the second project was to investigate the mechanisms underlying this increased susceptibility to severe outcomes following pH1N1/09 infection in morbidly obese individuals using primary human tissues. A case-control study design was adopted in which bronchial epithelial cells (hBECs), bronchoalveolar lavage (BAL) cells, peripheral blood mononuclear cells (PBMCs) and peripheral blood dendritic cells (DCs) were isolated from 15 morbidly obese individuals BMI $\geq$ 35 kg/m^2 and 15 age, gender and ethnicity-matched healthy weight ('lean') controls BMI 20-25 kg/m^2 by bronchoscopy and venesection to allow comparison of pro- inflammatory cytokine responses following pandemic and seasonal influenza infection.

Conclusions:

The PAVANE trial is not completed and data will be presented in future. We will present preliminary results in the meeting.

On the contrary, 15 patients have been included in the second study looking at influenza and obesity related poor outcome. Elevated leptin levels were observed in the lung and serum of the obese subjects, suggesting visceral fat was producing in response to calories intake. BAL cells from morbidly obese individuals exhibited deficient type I and III IFN responses. We report relatively high expression of the lesser-studied adipokines in the lung and nose of patients with BMI > 35 kg/m^2. Additionally, the acute phase protein, C-reactive protein (CRP), a biomarker of inflammation, was significantly elevated in the BAL fluid of the obese subjects.

In theory, obesity-associated BAL cell IFN deficiency may contribute to the increased susceptibility to severe outcomes seen in the obese population following influenza infection. On the contrary, pro-inflammatory cytokine protein levels are elevated in the airways and serum of obese individuals relative to those of healthy weight controls and this might justify the different response to bacterial infections. Consistent with our proposed model of the underlying mechanism, elevated leptin levels were observed in the lung and serum of the obese subjects. The exact mechanism by which obesity may result in BAL cell IFN-deficiency remains unclear. Nevertheless, this novel, obesity-associated

BAL cell IFN deficiency may contribute to the adverse outcomes seen in the obese population upon influenza infection.

References:

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