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Critical Rounds

MICRO LABS LIMITED

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Greetings from Micro Labs limited. We are happy to bring "CRITICONNECT" containing latest information in the field of Critical care medicine.

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Medical Team, Micro Labs Ltd

Role of Cytokines in COVID-19 management

Survival levels were slightly higher, while there was no gap in mechanical ventilation-free survival between hospitalized COVID-19 patients diagnosed with high-dose anakinra, an interleukin-1 receptor blocker, and those undergoing regular care only, a limited retrospective study showed in Italy.

Though total survival at 21 days was substantially higher for COVID-19 patients in the anakinra community relative to historical controls receiving just standard treatment (90 percent vs. 56 percent, P=0.009, respectively), the gap in mechanical ventilation-free survival between groups was not important, according to Giulio Cavalli, MD, of Vita-Salute San Raffaele University in Milan. The study may have been underpowered for the latter outcome, with 29 patients receiving anakinra and 16 controls. The authors noted that in 72 percent of cases, therapy with high-dose anakinra used to manage autoinflammatory conditions such as rheumatoid arthritis was effective and consistent with clinical progress, including changes in respiratory function and decreases in C-reactive protein, a sign of inflammation.

In a comment, Cavalli said this research is the first to indicate that a large dose of the anakinra arthritis medication could be able to prevent the overreaction of the COVID-19-induced immune system. However, the investigators reported an earlier phase III study that claimed anakinra in sepsis demonstrated substantial survival gain in hyperinflammatory patients. They noted that in contrast with other cytokine-blocking inhibitors, anakinra has an impressive safety record and a limited half-life, allowing for prompt discontinuance.

An additional editorial by Kate Kernan, MD, and Scott Canna, MD, both of Pittsburgh's Children's Hospital, observed prior work suggesting correlations between inflammatory biomarkers and ARDS growth and COVID-19 patient mortality.

Kernan and Canna wrote that these and other new research correctly concentrate more emphasis on the reactive reaction of the host, which may cause a change in how we treat the partnership between host which virus.

Researchers also observed that a more gradual and full increase in C-reactive protein in the anakinra population was followed by the higher 21-day survival rate, which was described as exceptional in a situation of 30-50 percent mortality in patients with clinical ARDS.

And while the editorialists noted that in this cohort both ferritin and C-reactive protein values were higher than in other COVID hospitalized adults, they correlated better with mortality risk, and thus could help identify a subset of patients who are most likely to benefit from anti-inflammatory treatments.

Cavalli and collaborators studied successive adult patients with COVID-19, mild to extreme acute respiratory distress syndrome (ARDS), and controlled non-invasive ventilation in the intensive care unit by hyperinflammation. 200 mg of hydroxychloroquine twice daily and 400 mg of lopinavir and 100 mg of ritonavir twice daily is normal care. Patients in the anakinra group received high-dose anakinra 5 mg/kg twice daily.

From March 17 to March 27, 29 patients prescribed high-dose anakinra, in addition to normal treatment. Median patient age was 62, males were more than 80 percent, and extreme ARDS was more than 85 percent. We were linked to a sample of 16 patients who did not seek anakinra in the past. Seven other patients obtained subcutaneous anakinra in small doses but their diagnosis was stopped after 7 days due to lack of progress. 21 patients in the high-dose population anakinra had changes in respiratory quality after 21 days compared with 10 out of 16 historical samples. Five patients versus one patient respectively needed artificial ventilation, and three patients died in the anakinra community against seven in the contrast category.

Notably, 13 were released from hospital in the anakinra community, although three no longer had supplementary oxygen, three got supplementary low-flow oxygen, and two no longer had ARDS. Seven were released from the hospital in the comparative sample, only one was also getting supplementary low-flow oxygen. For a total of 9 days, care was continued for adverse reactions in seven cases, with four developing bacteremia, primarily Staphylococcus epidermidis, while three reported changes in serum enzymes in the liver. Two patients in the reference community had bacteremia, and all five patients had elevated liver enzymes. Four people in the anakinra community had thromboembolism due to COVID-19 pathogenic cases, and two in the reference category.

Noting the study's multiple drawbacks, including its limited scale, its retrospective scope, the use of historical controls and restriction to a single location, Kernan and Canna said the results would be viewed as "exploratory," but also deserve more analysis. Provided the anakinra 's biological plausibility, the drug's pharmacokinetic and safety profile, and an increasing body of successful experience in autoinflammation and cytokine wind, such evidence pledge and encourage prioritizing this strategy in the preparation and recruitment of randomized controlled trials.

Source: Cavalli G, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol 2020; DOI: 10.1016/S2665-9913(20)30127-2.

The relationship of gut microbiome and mortality in trauma patients in the emergency department

INTRODUCTION

The microbiome is the ecological community of commensal, symbiotic, and pathogenic microorganisms that share our body space with a composition differentiated by body location. The gut acts as an inflammatory organ in accordance with the gut microbiome (GM), which affects the production and preservation of the immune system and, ultimately, inflammation, due to its connection to the external environment. Gut microbes defend the innate immune system against transiently invading pathogens by providing tonic stimulus through toll-like receptor signaling that increases intestinal motility, strengthens epithelial integrity and produces metabolites. Although developments in the complexity of human GM have recently been observed in a variety of disease states, in the case of traumatic injury very little is still understood. In a variety of ways, trauma may affect the intestine by actively damaging the intestine, interrupting the axis of the brain-gut, or by global hypoperfusion or inflammation. The impact on the intestine after physical injury in turn affects the GM and induces dysbiosis, or an anomaly or abnormal intestinal microbe distribution. Rapid dysbiosis has also been seen in serious disease, with deterioration through extended hospitalization, and septic problems have also been related. Although decreases in GM diversity have been related to increased mortality in critically ill patients, the effect of trauma on the microbial bowel population is poorly established.

In trauma patients there is a distinct dysbiosis likely to be linked to the vulnerability of this group to complications such as multiple organ failure (MOF), hospital-acquired infection, and systemic inflammatory reaction. Several early clinical studies have shown phylogenetic changes within gut microbial communities following traumatic and burn injuries in limited patient populations, but these studies lacked the capacity to consider clinically meaningful results.

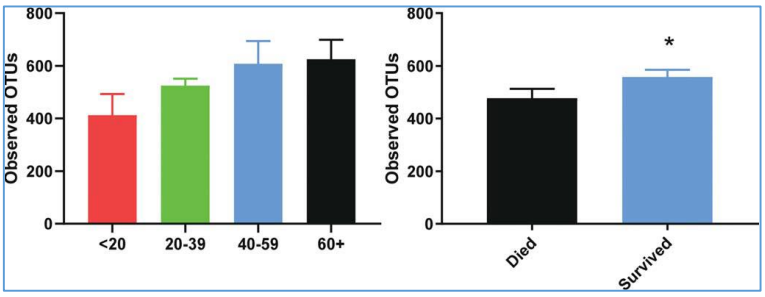
Preclinical evidence from different types of injuries, including polytrauma, burn damage, traumatic brain injury and spinal cord injury, further reinforce the hypothesis that severe injury changes the GM, which influences outcomes. Larger clinical trials are required to fill this discrepancy and further explain microbial modifications that arise in the intestine following injury and its connection to outcomes. The objective of this follow-up study was to determine if the GM is associated with clinical outcomes in critically injured patients

METHODS

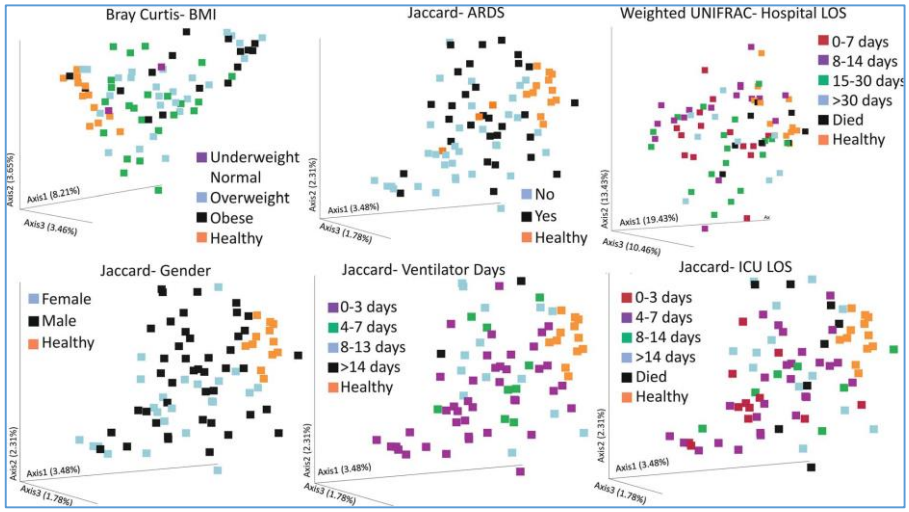
A prospective, observational study was conducted in adult patients (N = 67) sustaining severe injury admitted to a level I trauma center. Fecal specimens were collected on admission to the emergency department, and microbial DNA from all samples was analyzed using the Quantitative Insights IntoMicrobial Ecology pipeline and compared against the Greengenes database. α-Diversity and β-diversity were estimated using the observed species metrics and analyzed with t tests and permutational analysis of variance for overall significance, with post hoc pairwise analyses.

RESULTS

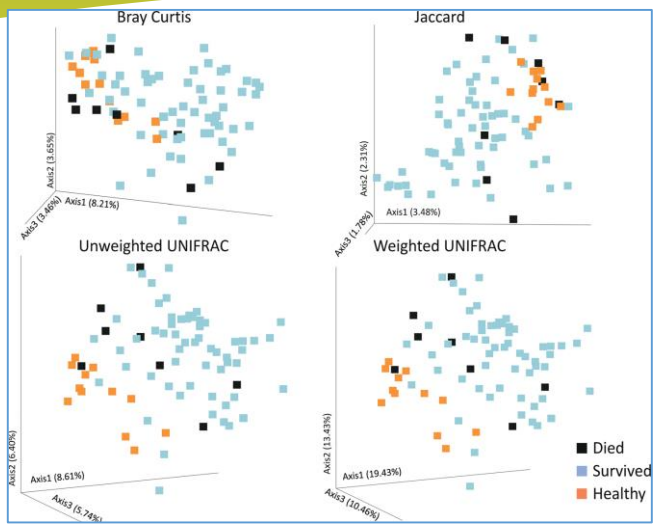
The patient population consisted of 63% males with a mean age of 44 years. Seventy-eight percent of the patients suffered blunt traumawith 22%undergoing penetrating injuries. Themean body mass indexwas 26.9 kg/m2. Significant differences in admission β-diversity were noted by hospital length of stay, intensive care unit hospital length of stay, number of days on the ventilator, infections, and acute respiratory distress syndrome ($p < 0.05$). β-Diversity on admission differed in patientswho died compared with patients who lived (mean time to death, 8 days). There were also significantly less operational taxonomic units in samples from patients who died versus those who survived. A number of species were enriched in the GM of injured patients who died, which included some traditionally probiotic species such as Akkermansia muciniphilia, Oxalobacter formigenes, and Eubacterium biforme ($p < 0.05$).



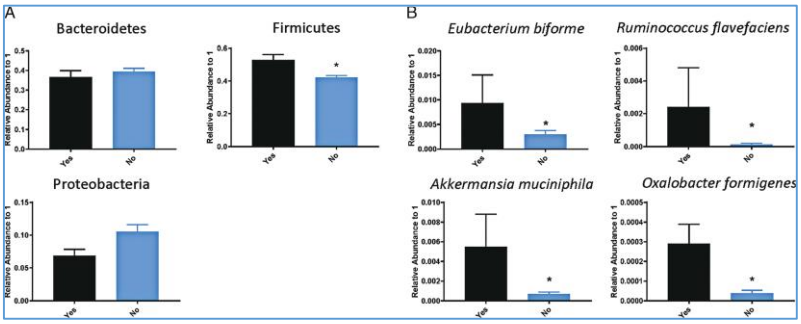
Operational taxonomic units demonstrating α-diversity for chosen patient characteristics. Statistical analyses reveal that OTUs increase with age (A) and in patients who died (B). *p < 0.05.



Significant findings in β-diversity measures for chosen patient characteristics. Bray-Curtis measures clustered different depending on BMI (A), while the weighted UniFrac clustered patients based upon their hospital LOS (B). The Jaccard similarity index was able to significantly cluster patients based on whether they experienced ARDS (C), sex (D), ventilator days (E), and ICU LOS (F). p < 0.05 for all plots.



β-Diversity plots for mortality. Patients who lived showed significantly different β-diversity than those who died for all β-diversity measures: Bray-Curtis (A), Jaccard (B), Unweighted UniFrac (C), and weighted UniFrac (D). p < 0.05 for all plots.



Phylogenetic differences associated with survival. (A) At the phylumlevel, levels of Bacteroideteswere unchanged,while levels of Firmicutes were significantly enriched in patients who died versus those that did not. (B) At the species level, there were four specific species (E. biforme, R. flavefaciens, A. muciniphila, andO. formigenes) thatwere enriched in the gutmicrobiota of patientswho died versus those that did not (p < 0.05).

CONCLUSIONS

The new study's awareness reflects the largest survey on trauma patients with GM to date. Mortality due to traumatic injury is correlated with a GM which involves less individual organisms but comprises a higher number of specific probiotic species that are commercially accessible. In comparison, all measures of β-diversity assessed were able to categorize patients according to whether or not they contributed to their injuries. Although there have been several of these measurements of diversity which have also been able to aggregate other significant findings, the particular correlations are not as strong as those between mortality and all parameters of β-diversity. Taken together, the GM holds great promise of diagnostic and therapeutic goals for traumatic injury, and more clinical and preclinical trials are required.

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Determination of Neurologic Death in Children by Transcutaneous Carbon Dioxide Monitoring During Apnea Testing

INTRODUCTION

Neurological death determination (NDD) in babies and children is a psychiatric condition focused on the lack of neurological activity with the coexistence of permanent coma and apnea. Global recommendations for DND in children provide medical requirements for two separate tests by physicians verifying coma and apnea coexistence. Apnea monitoring is assumed to be associated with neurological mortality if no involuntary respiratory activity is detected after Paco2 rises to greater than or equivalent to 60 mm Hg and reaches 20 mm Hg over baseline pretesting. Paco2 rates increase at a pace of around 3–5 torr per minute for patients who undergo DND apnea examination.

Providers receive sampling of arterial blood gas (ABG) at scheduled intervals (every 3–5 min) to record escalation to Paco2. If apnea monitoring cannot be performed securely due to hemodynamic dysfunction or respiratory decompensation, or if measures of blood gas cannot be collected accurately, DND needs an ancillary examination, such as an electroencephalogram or an analysis of cerebral blood flow radionuclides. Monitoring of noninvasive carbon dioxide (CO2) in chronically sick children is commonly done through automated intrusive and non-invasive ventilation. The most common modality, end-tidal capnography (Etco2), is calculated in the ventilation circuit and mostly used as a proxy for direct measurements of Paco2. But Etco2 depends on CO2 extraction from exhaled air and apnea monitoring involves a temporary mechanical ventilator disconnection. Just two findings from adults and no pediatric trials directly measured Tcco2 during DND apnea study. The study was done to determine the degree of correlation between paired transcutaneous carbon dioxide and Paco2 values during apnea testing for determination of neurologic death.

METHODS

Design: Single-center, retrospective case series.

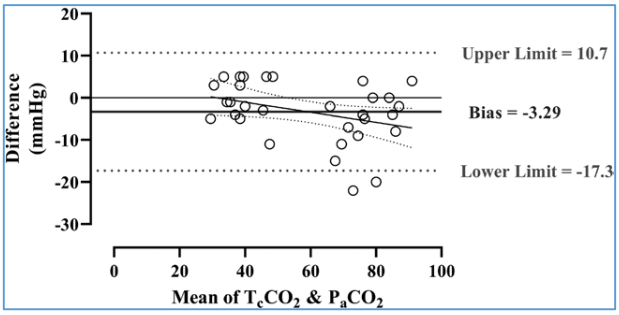
Setting: Twenty-eight bed PICU in a 259-bed, tertiary care, referral center.

Patients: Children 0–18 years old undergoing determination of neurologic death

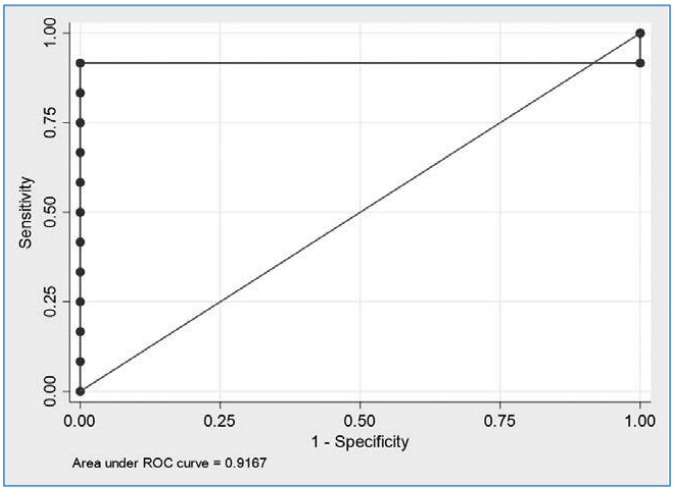
RESULTS

Primary outcomes were paired transcutaneous carbon dioxide and Paco2 values obtained during determination of neurologic death. Primary analyses included Pearson correlation coefficient, Bland-Altman bias and limits of agreement, and comparative statistics. Descriptive data included demographics, admission diagnoses, hemodynamics, Vasoactive Inotropic Scores, and arterial blood gas measurement. Eight children underwent 15 determination of neurologic death examinations resulting in 31 paired transcutaneous carbon dioxide and Paco2 values for study.

Transcutaneous carbon dioxide and Paco2 correlated well (r = 0.94; p < 0.01). Bias between transcutaneous carbon dioxide and Paco2 was –3.29 ± 7.14 mm Hg. Differences in means did not correlate with Vasoactive Inotropic Score (r = 0.2) or patient temperature (r = 0.11). Receiver operator characteristic curve of transcutaneous carbon dioxide after 3–10 minutes of apnea to discriminate positive apnea testing by the standard of Paco2 yielded an area under the curve of 0.91 and threshold of greater than or equal to 64 mm Hg (sensitivity, 91.7%; specificity, 100%; positive predictive value, 100%; negative predictive value, 92.3%; accuracy, 95.9%).



Bland-Altman plot for Paco2 versus transcutaneous partial pressure of carbon dioxide (Tcco2) with upper and lower limits of agreement and fitted regression with 95% confidence band.



Receiver operator characteristic (ROC) curve of transcutaneous carbon dioxide measurement after 3–10 min of apnea during determination of neurologic death examinations to discriminate between positive and negative apnea testing results using the standard of Paco2 blood sampling to document target Paco2.

CONCLUSIONS

Non-invasive transcutaneous carbon dioxide screening demonstrated strong consistency, precision, and limited bias as compared to Paco2 during apnea research for assessing neurological mortality in infants. Further testing is required before any suggestion can be made to substitute Paco2 with non-invasive transcutaneous carbon dioxide monitoring. Concurrent transcutaneous carbon dioxide results, however, will reduce excessive apnea period and associated hemodynamic instability or respiratory decompensation by approximating arterial goals.

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