thirty therapy was completely protective in mice depleted of a single effector. While dual depletion resulted in diminished MAb efficacy in terms of survival, mice retaining neutrophils had marked improvements in survival with MAb therapy compared with other dual-depletion groups. The dissociation of bacterial density and survival suggested that inflammation was a primary driver of host outcome. Levels of IL-10 and TNFα and a reciprocal relationship in mice across effector depletion groups and were lower in mouse groups with higher survival when adjusted for bacterial density. IL-10 disruption completely abrogated the survival benefit of MAb therapy without altering bacterial clearance mediated by MAb. In contrast, TNFα disruption enhanced MAb efficacy for survival, and the presence of TNFα was antagonistic to MAb efficacy for lethality. Thus, a dissociation of bacterial density and survival was observed. MAb or neutrophils did not impact bacterial density but macrophage depletion markedly reduced lethality but complement deficiency did. In contrast, singly disrupting complement resulted in reduced survival compared with placebo. We also raised a monoclonal antibody (MAb) that recognizes Mtb but has no effect on mouse survival. We note a decreased bacterial burden in Mtb-infected mice treated with placebo or anti-CD16/32, neutrophils with cyclophosphamide, and/or complement with anti-C5. These findings confirm that host outcomes from A. baumannii infection are driven by host inflammatory response rather than bacterial density alone. Furthermore, novel therapeutic approaches seeking to improve outcomes from such infections must seek to shift the balance of pro-/anti-inflammatory cytokines to favor a down-modulated inflammatory response.

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970. Antibiotic Use Variability Among US Nursing Homes—2016
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Session: 124. Out of the Box and Out of the Hospital: Stewardship Outpatient Services
Friday, October 4, 2019: 11:30 AM

Background. Antibiotics are frequently prescribed in nursing homes (NH). National data describing facility-level antibiotic use (AU) in NH are lacking. The objectives of this analysis were to use NH electronic health records (EHR) to describe AU in NH and variability in AU rates across NH.

Methods. We analyzed antibiotic orders from 309,884 residents in 1,664 US NHs using one EHR company in 2016. We calculated AU rates as antibiotic days-of-therapy (DOT) per 1,000 resident-days and compared by the type of stay (short-stay (SS) ≤ 100 days vs. long-stay (LS) > 100 days). We also examined prescribing indications and the duration of nursing home-initiated antibiotic orders. We assessed facility-level correlates of AU using resident health and NH facility characteristics publically available through NH Compare and LTCFocus using a univariate linear regression.

Results. In 2016, 57% of NH residents received at least one systemic antibiotic; overall rate of AU was 90 DOT/1,000 resident-days. The median facility-level DOT per SS resident was 64 DOT/1,000 resident-days (IQR 36–104). The median proportion of SS residents at a facility was 74% (IQR 68–90%). The SS and LS AU rates were 241 DOT/1,000 resident-days (IQR 173–342) and 24 DOT/1,000 resident-days (IQR 14–37), respectively. Overall, the three most common antibiotic classes prescribed were fluoroquinolones (18%), cephalosporins (18%), and extended-spectrum β-lactams (10%). Antibiotics were most frequently prescribed for urinary tract infections, and the mean duration of an antibiotic order was 9 days (range 1–365). Higher facility AU rate correlated positively with the following facility characteristics: proportion of SS residents, urban location, proportion of residents with mild cognitive impairment and lower activities of daily living scores, presence of ventilator beds, proportion of LS residents with urinary catheters or pressure ulcers, facility case-mix index, and for-profit ownership and multiorganization facilities.

Conclusion. Significant variability in NH AU rates exist, and SS residents have higher AU rates. Identifying NH with high rates of AU after adjusting for facility-level predictors of AU may identify opportunities for targeting efforts to improve prescribing practices.

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971. The Role of Inflammation and Innate Effectors in Passive Immunization for Acinetobacter baumannii Infections
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Session: 125. Pathogenesis and Inflammatory Response
Friday, October 4, 2019: 10:30 AM

Background. We have previously demonstrated that A. baumannii virulence is driven by avoidance of innate effector clearance, resulting in LPS-TLR4 triggering of excess inflammation in the host. We also raised a monoclonal antibody (MAb) that improved survival of mice lethally infected with A. baumannii.

Methods. Mice were selectively depleted of innate effectors (macrophages with liposomal clodronate, neutrophils with cyclophosphamide, and/or complement with cobra venom factor), infected with an XDR clinical blood isolate of A. baumannii, and treated with placebo or anti-A. baumannii MAb.

Results. Single disruption of macrophages or neutrophils did not enhance lethality but complement deficiency did. In contrast, singly disrupting complement or neutrophils did not impact bacterial density but macrophage disruption markedly increased it. Thus, a dissociation of bacterial density and survival was observed. MAb therapy was completely protective in mice depleted of a single effector. While dual depletion resulted in diminished MAb efficacy in terms of survival, mice retaining neutrophils had marked improvements in survival with MAb therapy compared with other dual-depletion groups. The dissociation of bacterial density and survival suggested that inflammation was a primary driver of host outcome. Levels of IL-10 and TNFα and a reciprocal relationship in mice across effector depletion groups and were lower in mouse groups with higher survival when adjusted for bacterial density. IL-10 disruption completely abrogated the survival benefit of MAb therapy without altering bacterial clearance mediated by MAb. In contrast, TNFα disruption enhanced MAb efficacy for survival, and the presence of TNFα was antagonistic to MAb efficacy for lethality. Thus, a dissociation of bacterial density and survival was observed. MAb or neutrophils did not impact bacterial density but macrophage depletion markedly reduced lethality but complement deficiency did. In contrast, singly disrupting complement or neutrophils did not impact bacterial density but macrophage disruption markedly increased it. Thus, a dissociation of bacterial density and survival was observed. MAb

Disclosures. All Authors: No reported Disclosures.

972. A Mycobacterium tuberculosis Secreted Lipid Triggers Cough Through a Neuronal Cough Receptor
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Session: 125. Pathogenesis and Inflammatory Response
Friday, October 4, 2019: 10:45 AM

Background. A hallmark symptom of active pulmonary tuberculosis vital for disease transmission is cough. The current paradigm for tuberculosis-related cough is that it results from airway damage or irritation. However, there is limited experimental data to underpin this theory, and whether Mycobacterium tuberculosis (Mtb) induces cough to facilitate its own transmission has not been explored. The cough reflex is a complex and coordinated event involving both the nervous and musculoskeletal systems initiated by particulate or chemical molecules activating nociceptive neurons, which sense pain or irritation. This activation induces a signaling cascade ultimately resulting in a cough. Respiratory nociceptive neurons innervate the airways of humans and most mammals and thus are poised to respond tonoxious molecules to help protect the lung from damage. Because Mtb is a lung pathogen, cough is a primary mechanism of Mtb transmission, and respiratory nociceptive neurons activate cough, we hypothesized that Mtb produces molecules that stimulate cough thereby facilitating its spread from infected to uninfected individuals. We previously identified a cough molecule produced by Mtb, and in this work characterize its neuronal receptor using genetics, biochemistry, and pharmacology.

Methods. We used an in vitro neuronal activation bioassay to study Mtb cough-inducing molecules. We also used a biochemical assay to identify the cough receptor. Finally, we used gene silencing, biochemistry, and pharmacologic inhibition to validate and characterize the activity of the newly discovered cough receptor.

Results. We isolated a complex lipid produced by Mtb that activates nociceptive neurons. Both an organic Mtb extract and the purified molecule alone were sufficient to induce cough in a conscious guinea pig cough model and guinea pigs infected with wild-type Mtb cough much more frequently than guinea pigs infected with Mtb strains unable to produce nociceptive molecules. Using genetics, biochemistry, and pharmacology techniques, we identified and validated a cough receptor for the Mtb lipid expressed on nociceptive neurons.

Conclusion. We conclude that Mtb produces a molecule that activates nociceptive neurons and induces cough through a specific neuronal receptor. These findings have significant implications for our understanding of Mtb transmission.

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multiple cellular populations in our organisms, including neuroprogenitor cells, inter-
mediate progenitor cells, and terminally differentiated neurons. We detect and quantify
host mRNA transcripts and viral RNA with single-cell resolution, defining transcrip-
tional features of uninfected cells and infected cells.

Results. In this model of the developing brain, we identify preferred tropisms of
ZIKV infection and pronounced effects on cell division, differentiation, and death.
Our data additionally reveal differences in cellular populations and gene expression
within organisms infected by historic and contemporary ZIKV strains from a variety of
geographic locations. This finding might help explain phenotypic differences attributed
to the viruses, including variable propensity to cause microcephaly.

Conclusion. Overall, our work provides insight into normal and diseased human
brain development, and suggests that both virus replication and host response mecha-
nisms underlie the neuropathology of ZIKV infection.

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974. PD-1 Immune Checkpoint Blockade Improves Survival and Promotes Fungal
Clearance in an Immunosuppressed Murine Invasive Pulmonary Aspergillosis
(IPA) Model
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Session: 125. Pathogenesis and Inflammatory Response
Friday, October 4, 2019: 11:15 AM

Background. Checkpoint blockade (CPB) has brought a revolution in
modern oncology and may offer new strategies for antifungal immunotherapy.

In vitro studies have demonstrated that blockade of the PD-1/PDL-1 interac-
tion increased IFN-γ secretion in response to Aspergillus antigens, suggesting a
potential role for anti-PD-1 therapy in promoting anti-Aspergillus immunity.
We sought to evaluate the therapeutic efficacy of low-dose anti-PD-1 therapy in a
murine IPA model.

Methods. Eight- to twelve-week-old female BALB/c mice were immunosup-
pressed with cyclophosphamide and cortisone acetate and infected intra-nasally
with 5 × 104 A. fumigatus AF293 conidia (panel A). Mice were then treated in-
tra-peritonally with 4 doses of either 200 µL PBS (PBS control), 250 µg/kg BW IgG
antibody (isotype control), or a monoclonal PD-1 antibody (anti-PD-1). Survival was
monitored daily until day 8 post-infection. 24–28 mice per treatment were
assessed in 3 independent experiments. Pulmonary fungal burden was determined
in infected mice (median spore equivalent: 0.39 vs. 2.06
106; P = 0.015). No signs of
toxicity or early mortality were seen in anti-PD-1–treated mice, and no elevated serum
levels of pro-inflammatory cytokines TNF-α and INF-γ were found in those mice
(compared with isotype–treated infected mice).

Conclusion. We found that anti-PD-1 immune checkpoint blockade has inde-
pendent beneficial effects in untreated immunosuppressed mice with IPA. We are in
the process of measuring pulmonary cytokines to deepen our understanding of protec-
tive anti-Aspergillus immunity conferred by low-dose CPB. In addition, future studies
would address the combined application of CPB and conventional antifungal drugs
that have immune-regulatory activity such as echinocandins.

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975. Roles of Type I and III Interferon in Severe Pathogenesis of Human
Metapneumovirus
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Session: 125. Pathogenesis and Inflammatory Response
Friday, October 4, 2019: 11:30 AM

Background. Human metapneumovirus (HMPV) is a leading cause of respira-
tory tract infection in children and adults. However, mechanisms of pathogenesis are
not fully understood.

Methods. We tested HMPV clinical and laboratory isolates in an established
c57BL/6 mouse model and measured weight loss, airway function, and viral titer.

Immune responses were determined using cytokine quantitation and flow cytometry.

Results. HMPV clinical isolates induced variable disease severity ranging from mild
to fatal disease. Laboratory strain TN94/49 did not cause weight loss, but mice infected
with clinical isolate C2-202 showed dramatic weight loss and 40% mortality within 5 days
post-infection (Figure 1). These findings were confirmed in other inbred mouse strains.

C2-202-infected mice also suffered from impaired pulmonary function post-recovery.
Lung viral titer did not correlate with disease severity, suggesting immune-mediated
pathogenesis. C2-202-infected mice exhibited increased production of type I and III inter-
erons (IFN) and pro-inflammatory cytokines, and lung neutrophil infiltration. However,
neutrophil depletion or inflammasome inactivation did not reduce disease. Stat1/Stat2
double knockout (KO) mice lacking type I and III IFN signaling exhibited reduced weight
loss but unchanged lung viral titer (Figure 2), while the addition of type III IFN blockade to C2-202-infected IFNAR
mice had no effect on disease but increased lung viral titer (Figure 4).

Conclusion. These results suggest that severe disease caused by virulent HMPV
was due to exuberant IFN response. Furthermore, type I IFN was primarily associated
with disease, while type III IFN was associated with viral clearance. These data suggest
that IFN signaling plays an important role in HMPV pathogenesis, and thus serves as
a potential therapeutic target.

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