Table. Antiviral activity of A218 and Vap against RV/EV infection.

| Virus types | A218 | Vap |
|-------------|------|-----|
| RV-A18      | 63   | 3.6 |
| RV-A16      | 44   | 37  |
| RV-A39      | 45   | 3.2 |
| RV-A45      | 42   | > 1,000 |
| RV-B14      | 73   | 30  |
| RV-B52      | 77   | 34  |
| RV-B69      | 43   | 33  |
| RV-C15      | 19   | > 10,000 |
| EV-A71      | 41   | 7,300 |
| CV-A6       | 66   | 340 |
| EV-B3       | 53   | > 10,000 |
| CV-B4       | 25   | 4,000 |
| EV-D68      | 60   | 210 |

Figure. Therapeutic effect of A218 on survival rate in CVB3-infected mice.

Conclusion. A218 is a promising therapeutic agent for improving the exacerbation of pathological conditions caused by RV infection. Nonclinical package including GLP-Toxo also supports the ongoing first-in-human study of A218.

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Session: O-28. Practice Issues

Background. In October 2015, CMS began requiring U.S. hospitals to report compliance with the Severe Sepsis/Septic Shock Early Management Bundle (SEP-1). We evaluated the impact of SEP-1 implementation on sepsis treatment patterns and outcomes using detailed clinical data from diverse hospitals.

Methods. We conducted a quasi-experimental interrupted time-series analysis of adults admitted to 114 hospitals in the Cerner HealthFacts dataset from October 2013-December 2017 with suspected sepsis (defined by blood culture orders, SIRS criteria, and acute organ dysfunction) within 24 hours of hospital arrival. The primary outcome was quarterly short-term mortality rates (in-hospital death or discharge to hospice). Secondary outcomes included lactate testing and administration of anti-MRSA or anti-Pseudomonal beta-lactam antibiotics within 24 hours of hospital arrival. Generalized estimating equations with robust sandwich variances were used to fit logistic regression models to assess for immediate SEP-1 impact and changes in quarterly trends after October 2015, adjusting for baseline characteristics and severity-of-illness.

Results. The cohort included 117,510 patients with suspected sepsis on admission. Lactate testing rates increased over the study period (61.9% pre-SEP-1 vs 77.9% post-SEP-1) with a significant immediate increase in risk-adjusted testing rates after SEP-1 (OR 1.34, 95% CI 1.04-1.74) (Figure 1). There was also an increase in utilization of anti-MRSA (20.6% pre vs 23.2% post-SEP-1) and anti-Pseudomonal antibiotics (30.1% vs 39.8%), but these trends began before SEP-1 implementation. Unadjusted short-term mortality was similar in the pre vs post-SEP-1 periods (20.3% vs 20.4%). SEP-1 was not associated with either an immediate change (OR 0.94, 95% CI 0.68-1.28) or quarterly trend change (OR 1.00, 95% CI 0.97-1.04) in risk-adjusted short-term mortality (Figure 2).

CDC Prevention Efficacies

Session: O-27. Novel Antimicrobial Agents

Background. Rhinovirus (RV) is a major respiratory virus that poses a threat to immunocompromised people and those with underlying disease. However, there are no approved therapies. Moreover, RV infection cannot be prevented by a vaccine because there are over 100 serotypes. Here we report the pharmacological profile of a novel small molecule host-targeted antiviral (HTA), KRP-A218 (A218). A highly potent and selective inhibitor of phosphatidylinositol 4 kinase beta (PI4KB), a key host factor of RV replication, A218 is undergoing clinical study.

Methods. In vitro antiviral activities of A218 and Vapendavir (Vap), a virus-targeted antiviral, were examined by inhibition of CPE, viral load, or replication. In vivo antiviral activity and pathological analysis of A218 were examined in coxsackievirus B3 (CVB3; belong to the genus enterovirus as with RV)-infected mice as a surrogate model of RV infection as CVB3, unlike RV, replicates very well in both mouse and human tissue. Daily oral dosing of A218 (1-10 mg/kg) was started 2 days post intra-peritoneal infection with RV. Tissue viral load, pancreas pathological change at 4 days post infection, and survival rate up to 14 days were evaluated. PI4KB heterozygous kinase-dead mice (PI4KB KD) were established by a CRISPR-Cas9 system. Viral load and survival rate following viral infection were evaluated in these mice.

Results. A218 showed antiviral activity for RV and enteroviruses (Table) and has a higher barrier to drug resistance than Vap. These results are consistent with expectations for HTAs. Repeated dosing of A218 starting 2 days post infection decreased viral load and improved acute pancreatitis, accompanied by decrease of inflammatory and pancreatitis markers in plasma. Moreover, therapeutic dosing of A218 improved survival rate in a CVB3-infected lethal mouse model (Figure). These results show the first evidence that a PI4KB inhibitor has potent therapeutic efficacy in a severe viral infection model. Similar effects were observed in PI4KB KD, supporting the on-target effect of A218.

134. KRP-A218, an Orally Active and Selective PI4KB Inhibitor with Broad-Spectrum Anti-Rhinovirus Activity, Has Potent Therapeutic Antiviral Activity In vivo

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Figure 1. Quarterly risk-adjusted rates of A) lactate testing, B) anti-MRSA antibiotic administration, and C) anti-Pseudomonal beta-lactam antibiotic administration within 24 hours of hospital presentation for patients with suspected sepsis before and after SEP-1 implementation in Q4 2015.

Table 1. Weekly Laboratory Monitoring of Antimicrobials (%)

| Antimicrobial | CBC | BMP | Liver | Other |
|---------------|-----|-----|-------|-------|
| Beta-lactams (n=68) | 92.2 | 90.5 | 83.2 | – |
| Daptomycin (n=5) | 96.7 | 96.7 | – | CPK: 96.7 |
| Vancomycin (n=18) | 94.4 | 95.8 | – | Trough: 88.5 |
| Micafungin (n=1) | 100.0 | 100.0 | 100.0 | – |
| Post-Total (n=92) | 93.0 | 92.1 | 83.6 | 90.7 |
| Pre-Total (n=91) | 63.2 | 63.3 | 49.5 | 73.5 |
| p-value | <0.001 | <0.001 | <0.001 | 0.087 |

Figure 2. Adherence to IDSA Guideline Follow-up Recommendation

Table of values for each parameter:

- ID consult prior to discharge: Pre (n=83) 36 (43.4), Post (n=77) 77 (100), p-value = 0.001
- Follow-up visit within 7-14 days of discharge: Pre (n=83) 26 (31.3), Post (n=77) 72 (93.5), p-value = 0.001
- Follow-up after completing OPAT: Pre (n=83) 51 (61.4), Post (n=77) 67 (87.0), p-value = 0.003

Figure 3. Rates of Clinical Cure

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