2296. Hypoglycemia Risk with Antibiotics: An Epidemiologic Surveillance Study of the FDA Adverse Event Reporting System (FAERS)

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Session: 246. Clincal Outcomes of Infections with Resistant Organisms
Saturday, October 5, 2019: 12:15 PM

Background. In July of 2018, the FDA published a drug safety warning for the potential risk of developing hypoglycemia with fluoroquinolones. Some studies have evaluated the potential risk of developing hypoglycemia with linezolid and tigecycline. A few case reports have also been published that report hypoglycemia from cefditoren, doxycycline, and trimethoprim-sulfamethoxazole use. Since data comparing various antibiotics and the risk of developing hypoglycemia is limited, the objective of this study was to evaluate the association between hypoglycemia and antibiotics using the FDA Adverse Event Reporting Systems (FAERS).

Methods. FAERS reports from January 1, 2004 to December 31, 2017 were included in the study. The Medical Dictionary for Regulatory Activities (MedDRA) was used to identify cases of hypoglycemia. Reporting odds ratios (RORs) and corresponding 95% confidence intervals (95% CI) for the association between antibiotics and hypoglycemia were calculated. An association was considered to be statistically significant when the lower limit of the 95% CI was greater than 1.0.

Results. A total of 2,334,959 reports (including 18,466 hypoglycemia reports) were considered, after inclusion criteria were applied. Cefditoren had the greatest proportion of hypoglycemia reports, representing 10% of all cefditoren reports. Statistically significant hypoglycemia RORs (95% CI) for antibiotics were: cefditoren 14.03 (8.93–22.03), tigecycline 3.32 (1.95–5.65), clarithromycin 2.41 (1.89–3.08), ertapenem 2.07 (1.14–3.75), moxifloxacin 2.06 (1.59–2.65), levofloxacin 1.66 (1.37–2.01), linezolid 1.54 (1.07–2.20).

Conclusion. Cefditoren, tigecycline, clarithromycin, ertapenem, moxifloxacin, levofloxacin, and linezolid were all significantly associated with hypoglycemia. The ertapenem association had not been reported in prior literature. Levofloxacin and moxifloxacin were the only fluoroquinolones significantly associated with hypoglycemia, even though the FDA drug safety warning was issued for all fluoroquinolones. Doxycycline and trimethoprim-sulfamethoxazole were not significantly associated with hypoglycemia, even though case reports have reported hypoglycemia with doxycycline and trimethoprim-sulfamethoxazole.

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2297. Epidemiology of Antibiotic-resistant Pathogens and Empiric Treatment Patterns in Community-Onset Sepsis

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Session: 246. Clincal Outcomes of Infections with Resistant Organisms
Saturday, October 5, 2019: 12:15 PM

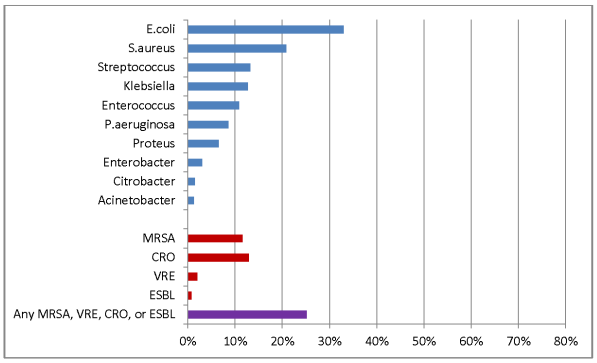
Background. Guidelines recommend immediate empiric broad-spectrum antibiotics for all patients with suspected sepsis. Understanding the epidemiology of antibiotic-resistant pathogens and empiric treatment patterns in sepsis could inform improvements in antibiotic utilization and outcomes.

Methods. We identified adults admitted during 2009–2015 to 104 US hospitals in the Cerner HealthFacts dataset who met CDC Adult Sepsis Event criteria and had positive clinical cultures within 2 days of admission. We characterized prevalence and empiric treatment rates for methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococcus (VRE), ceftriaxone-resistant Gram-negative organisms (CRO) (including *P. aeruginosa*), and extended-spectrum β-lactamase Gram-negative organisms (ESBL). We evaluated associations between in-hospital mortality and either inappropriate empiric therapy (antibiotics inactive against any isolated pathogen) or excessively broad therapy (empiric MRSA or VRE coverage, extended spectrum β-lactam, or carbapenem therapy when targeted organisms were absent), adjusting for baseline characteristics and severity-of-illness.

Results. The cohort included 17,962 patients with culture-positive sepsis; 2,965 (16.5%) died in-hospital. The most common culture-positive sites were urine (51.2%), blood (41.8%), and respiratory (16.5%). The most common pathogens were *E. coli* (33.0%), *S. aureus* (20.9%), and Streptococcus (13.2%) (Figure 1). Most (81.6%) patients received empiric antibiotics active against all isolated pathogens. Empiric therapy was directed at resistant organisms in 67.5% of cases (primarily vancomycin and extended spectrum β-lactams, Figure 2), but resistant organisms were isolated in only 25.2% (MRSA 11.5%, CRO 12.9%, VRE 2.0%, ESBL 0.8%). Both inappropriate empiric therapy and excessively broad empiric therapy were associated with higher mortality on multivariate analysis (OR 1.30, 95% CI 1.14–1.48 and OR 1.20, 95% CI 1.05–1.38, respectively).

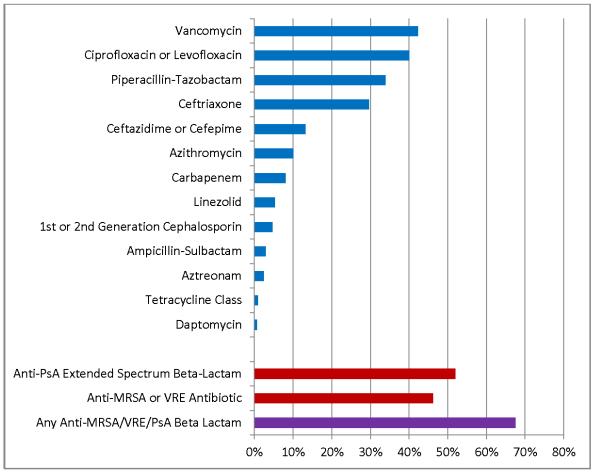
Conclusion. Most patients with community-onset sepsis do not have resistant pathogens, yet empiric broad-spectrum antibiotics are frequently prescribed. Both inappropriate empiric therapy and excessively broad therapy are associated with worse outcomes.

Figure 1. Distribution of pathogens and resistant organisms in patients with community-onset sepsis and positive clinical cultures



MRSA = methicillin-resistant *Staphylococcus aureus*; CRO = ceftriaxone-resistant gram negative organism (including *Pseudomonas aeruginosa*); VRE = vancomycin-resistant enterococcus; ESBL = extended spectrum beta-lactamase producing gram negative organism (defined by phenotypic resistance to all beta-lactams except carbapenems).

Figure 2. Frequency of administration of empiric antibiotics in patients with community-onset sepsis and positive clinical cultures



Carbapenems include imipenem, meropenem, doripenem, and ertapenem. Anti-PsA (Pseudomonal) extended spectrum beta-lactams include ceftazidime, cefepime, piperacillin-tazobactam, aztreonam, imipenem, meropenem, and doripenem. Anti-MRSA or VRE antibiotics include vancomycin, linezolid, and daptomycin.

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2298. Infections in Patients Receiving TVEC Therapy

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Background. Oncolytic viral immunotherapy is an emerging cancer treatment, but the infectious complications are not well described outside of clinical trials. Genetically engineered replication competent herpes simplex virus (HSV-1), commercially known as IMLGYIC® (AmGen) or talimogene laherparepvec (TVEC) was the first FDA approved agent in this class and is used for the local intralesional treatment (of unresectable melanoma. TVEC is derived from a wild-type(WT) strain of HSV-1 (JS—1), which is modified to attenuate off-target effects and promote selective proliferation within cancer cells. Despite these changes local and systemic infection with HSV have been reported from trials and is the subject of an FDA mandated post-marketing review. Here we review the infectious complications of the first cohort of patients treated at our institution post-FDA approval.

Methods. Demographic and clinical information for 52 adult patients treated for unresectable melanoma with TVEC following FDA approval in 2015 was extracted from the EMR for the period October 1, 2015–June 30, 2018. EMR and microbiologic data were reviewed for evidence of local site reaction and disseminated infection.

Results. No cases of disseminated HSV infection were identified during the study period. Of cutaneous reactions, none were documented as greater than severity grade 2, based on standard adverse event reporting criteria. 3 (50%) grade 1–2 cutaneous reactions were deemed probable or definitely related to TVEC and described as pruritis or rash. 12 (23%) patients had any microbiologically confirmed infection identified following TVEC therapy; 6 were bacterial (3 UTI, 1BSI, 2 wound). 8 episodes of viral infections occurred (5 respiratory and 3 GI). A single patient was noted to have localized HSV dermal lesions more than one year after the final TVEC.

Conclusion. No local or disseminated HSV infections were encountered in the study cohort. Bacterial skin and soft-tissue infection were uncommon. Most other infections were unrelated to TVEC therapy. Real-world review of the use of an HSV-derived oncolytic viral vector therapy mimics reported infectious complications from clinical trials.

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2299. A London Hospital's Experience of Confirmed Measles Infections and Re-Infections Between 2009 and 2019

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Session: 247. Clinical Virology/Viral Epidemiology
Saturday, October 5, 2019: 12:15 PM

Background. 2018 to 2019 has seen a global resurgence in measles cases, with the UK seeing an over 3-fold increase in cases in 2018 compared with 2017. In this context, our center saw a cluster of geographically linked measles cases presenting in the first quarter of 2019. We present this with comparative data of confirmed measles cases from our center over the preceding 10 years. Given the growing recognition of measles "re-infection" in fully vaccinated individuals, we also present our first confirmed cases of reinfection within this cohort.

Methods. Retrospective analysis of confirmed measles cases (positive Measles IgM or detectable Measles RNA) between 2009 and 2019. Laboratory and demographic data were obtained from electronic patient records.

Results. 18 cases (of which 14 were adults) of measles (all genotype D8 of those tested) were confirmed in the first 4 months of 2019. 12 presented within a 14 day period from a geographically linked part of North London. There were 4 confirmed measles re-infections (detectable measles RNA on a buccal swab with either a high Measles IgG avidity or previous documented measles immunity). From the 10 year data, cases peaked in 2011 and 2016 consistent with national trends. Of the 89 cases identified, 60 (67%) were adults, who were over twice as likely to be admitted as children, had a longer median length of stay in hospital (2 days vs. 1.5 days) and were more likely to develop a hepatitis (1/10 pediatric cases vs. 26/48 adults, $p \leq 0.01$)or other complications. The majority of adults (68%) were unsure of their vaccination status.

Conclusion. 4 cases of 18 in the first 4 months of 2019 were confirmed re-infections. Re-infections in fully vaccinated individuals are described in the literature, typically presenting with a milder course; however, these are the first cases we have identified at our center. Overall, adult cases were more likely to be admitted to hospital and to have a complicated course compared with children. Vaccination history in adults was of limited clinical utility due to lack of reliable documentation and the potential for reinfection.

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2300. Incidence, Complications, and Recurrence of Herpes Zoster in Unvaccinated Adults ≥50 Years of Age

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Session: 247. Clinical Virology/Viral Epidemiology
Saturday, October 5, 2019: 12:15 PM

Background. More recent baseline epidemiological data for Herpes Zoster (HZ) in adults ≥ 50 years of age, obtained before the introduction of the adjuvanted Recombinant Zoster Vaccine (RZV), are needed for future evaluations of the impact of RZV on HZ epidemiology.

Methods. The study comprised five elements: (1) The incidence of HZ was estimated from immunocompetent adults ≥ 50 years of age not vaccinated with Zoster Vaccine Live who had incident HZ between 2011–2015. HZ was identified by International Classification of Diseases (ICD) codes from electronic health records (EHR) of 4.6 million Kaiser Permanente Southern California members; (2) Postherpetic neuralgia (PHN) was identified by validated survey and medical record review of laboratory-confirmed incident HZ cases recruited during 2012–2015 for HZ-related pain ≥ 90 days after initial HZ diagnosis; (3) HZ Ophthalmicus (HZO) with ocular complications was identified by ICD codes and keyword search in EHR among patients identified with HZO using a validated natural language processing algorithm; (4) The proportion of HZ-related non-PHN and non-HZO cutaneous, neurological or other complications was assessed by double abstraction of EHRs from a sample of 600 incident HZ cases; (5) Recurrent HZ was identified by having an HZ diagnosis with HZ antiviral medication ≥ 6 months after the most recent HZ diagnosis with HZ antiviral medication in a cohort initially diagnosed with HZ between 2007 and 2008 and followed through 2016.

Results. We identified 40,893 incident HZ cases with an overall incidence of 9.92 (95% confidence interval [CI]: 9.82–10.01) per 1000 person-years. The proportion of incident HZ cases with PHN and HZO with ocular involvement was 18.37% (95% CI: 14.90–21.84%) and 8.06% (95% CI: 7.80–8.32%), respectively. The proportion of cutaneous, neurological, and other complications was 7.20% (95% CI: 5.44–8.96%), 0.87% (95% CI: 0.79–0.95%), and 1.24% (95% CI: 1.15–1.33%), respectively. The incidence of recurrent HZ was 10.96/1000 person-years (95% CI: 10.18–11.79).

Conclusion. HZ is common among unvaccinated US adults ≥ 50 years of age, with PHN and HZO occurring most frequently among incident HZ cases.

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2301. Increased Risk of Varicella-Associated Hospitalizations Among Adult Immigrants From Temperate and Tropical Countries After the Introduction of a Childhood Varicella Vaccination Program in Quebec, Canada

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Session: 247. Clinical Virology/Viral Epidemiology
Saturday, October 5, 2019: 12:15 PM

Background. Varicella zoster virus (VZV) hospitalizations are an uncommon, severe and costly consequence of VZV. Childhood VZV vaccination leads to decreased VZV rates across all age groups through herd immunity but increases the age of VZV acquisition and the potential risk of severe VZV in non-immune adults. A large proportion (~15%) of young adult immigrants from tropical regions are susceptible to VZV due to different transmission dynamics in their countries of origin and lack of vaccination. We aimed to describe the impact of the childhood VZV program introduced in 2006 in Quebec on VZV hospitalizations in immigrants and nonimmigrants.

Methods. A population-based cohort of all medically-attended VZV cases in Quebec, Canada (1996–2014) were identified in administrative health databases and linked to immigration data. VZV-attributable hospitalizations included those with primary or secondary ICD-9 or ICD-10 codes for VZV. Overall age-standardized and age-specific rates of hospitalizations were calculated during pre- (1996–98), private (1999–2005) and public vaccination (2006–14) periods and by immigrant status and pregnancy. Relative risk ($RR_{I\text{-}NI}$) and 95% CI for immigrants vs. nonimmigrants were estimated.

Results. 5873 hospitalizations occurred among 230,052 VZV cases. Hospitalization rates decreased dramatically in the pre to public vaccination period (6.6 to 1.3/100,000 population); however, the proportion of hospitalized varicella cases increased from 1.7% to 3.9% ($P < 0.01$). Immigrants only accounted for 3.6% of hospitalizations ($N = 213$) however, the proportion of all hospitalizations among immigrants increased in the pre- vs. public-vaccination periods in those aged 10–19 years (2.9% to 13.7%) and 20–39 years (8.8% to 22.7%). The RR was higher in these age groups in the public vaccination period [$RR_{I\text{-}NI}$ 1.96 and $RR_{I\text{-}NI}$ 1.67] (Table 1). Adults (>20 years) accounted for 52% (CI: 45–59%) and pregnant women 18% (13–25%) of all hospitalizations among immigrants compared with only 14% (13–15%) and 1.6% (1.3–2.0%) in nonimmigrants, respectively.

Conclusion. Young adult and pregnant immigrants bore a disproportionate burden of VZV hospitalizations after the introduction of childhood VZV vaccination. Susceptible immigrant adults would benefit from targeted VZV vaccination.

Table 1: Overall age-standardized and age-specific rates of varicella attributable hospitalizations and proportion of cases by immigrant status in Quebec, Canada (1996-2014)

		Immigrants			Non-Immigrants			Immigrants vs non-Immigrants
Age-group	Vaccination Period	Cases N	% cases [row] (95% CI)	Rate per 100,000	cases	% cases [row] (95% CI)	Rate per 100,000	Rate Ratio$_{I\text{-}NI}$ (95%CI)
0-9 years	1996-1998	16	1.2 (0.6-1.8)	23.0 (14.1 - 37.6)	1322	98.8 (98.2-99.4)	50.7 (48.0 - 53.5)	0.45 (0.28 - 0.74)
	1999-2005	49	1.8 (1.3-2.3)	26.2 (19.8 - 34.7)	2665	98.2 (97.7-98.7)	48.0 (46.2 - 49.8)	0.55 (0.41 - 0.72)
	2006-2014	20	2.9 (1.6-4.1)	6.1 (4.0 - 9.5)	678	97.1 (95.9-98.4)	9.6 (8.9 - 10.3)	0.64 (0.41 - 1.00)
10-19 years	1996-1998	2	2.9 (0.0-7.0)	1.3 (0.3 - 5.3)	66	97.1 (93.0-100.0)	2.5 (1.9 - 3.1)	0.53 (0.13 - 2.17)
	1999-2005	8	9.6 (3.3-16.0)	2.1 (1.0 - 4.2)	75	90.4 (84.0-96.7)	1.2 (1.0 - 1.5)	1.70 (0.82 - 3.53)
	2006-2014	7	13.7 (4.3-23.2)	1.1 (0.5 - 2.4)	44	86.3 (76.8-95.7)	0.6 (0.4 - 0.8)	1.96 (0.88 - 4.34)
20-39 years	1996-1998	18	8.8 (4.9-12.7)	2.8 (1.8 - 4.5)	187	91.2 (87.3-95.1)	3.3 (2.8 - 3.8)	0.87 (0.54 - 1.42)
	1999-2005	44	13.3 (9.7-17.0)	2.8 (2.1 - 3.7)	286	86.7 (83.0-90.3)	2.3 (2.1 - 2.6)	1.18 (0.86 - 1.62)
	2006-2014	20	22.7 (14.0-31.5)	0.8 (0.5 - 1.2)	68	77.3 (68.5-86.0)	0.5 (0.4 - 0.6)	1.67 (1.02 - 2.76)
40+ years	1996-1998	5	9.3 (1.5-17.0)	0.4 (0.2 - 1.0)	49	90.7 (83.0-98.5)	0.6 (0.5 - 0.8)	0.70 (0.28 - 1.76)
	1999-2005	13	10.5 (5.1-15.9)	0.4 (0.2 - 0.7)	111	89.5 (84.1-94.9)	0.5 (0.4 - 0.6)	0.81 (0.45 - 1.44)
	2006-2014	11	9.2 (4.0-14.3)	0.2 (0.1 - 0.4)	109	90.8 (85.7-96.0)	0.4 (0.3 - 0.4)	0.61 (0.33 - 1.14)
Total (ASR)	1996-1998	41	2.5 (1.7-3.2)	4.2 (2.5 - 5.8)	1624	97.5 (96.8-98.3)	6.7 (6.4 - 7.0)	0.63 (0.42 - 0.93)
	1999-2005	114	3.5 (2.9-4.1)	4.9 (3.8 - 6.0)	3137	96.5 (95.9-97.1)	6.1 (5.9 - 6.4)	0.79 (0.63 - 0.99)
	2006-2014	58	6.1 (4.6-7.6)	1.0 (0.7 - 1.4)	899	93.9 (92.4-95.5)	1.3 (1.3 - 1.4)	0.78 (0.57 - 1.06)

* 1996-1998 = pre-vaccination, 1999-2005 = private vaccination, 2006-2014 = public vaccination, ASR=age-standardized rate

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2302. A Meta-Analysis of Risk Factors for Herpes Zoster Infection

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Background. The burden of herpes zoster (HZ) is significant worldwide, with millions affected and the incidence rising. Current literature has identified some risk factors for this disease; however, there is yet to be a comprehensive study that pools