

Adverse Events Associated with Fluoroquinolone and Macrolide in Adult Outpatients treated for Community Acquired Pneumonia.

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Rationale

- Current (2007) US CAP guidelines provide direction on antibiotic selection in the outpatient setting.
- Each of the antibiotics recommended for CAP are associated with “adverse events of special interest” these are termed AESI.
- Prescription of antibiotics must be a consideration of risk: benefit.
- Thus large-scale, “real-world” data are needed to better understand such AESI and use this information to optimize antibiotic choice.

Rationale for Fluoroquinolone & Macrolide Focus

- ◆ These 2 classes account for almost 80% of all antibiotics written in primary care for diagnosed CAP in USA
- ◆ AEs occur more often in community setting than generally perceived but often overlooked and under reported.
- ◆ Recent regulatory and literature actions have drawn several AEs to wider, often public attention.
- ◆ AESI
 - ◆ Ventricular tachycardia, tachycardia, jaundice, elevated LFTs, liver failure, tendonitis, tendon rupture, neuropathy, neuritis and *Clostridium difficile*.
 - ◆ All AEs identified by ICD-9 codes and compared between treatment groups.

Truven Dataset – Background and Design

- ◆ Truven Health MarketScan Commercial Claims and Encounters Database and Medicare Supplemental and Coordination Benefits Database
- ◆ Includes data containing medical and drug claims for over 40 million individuals annually including 4.3 million Medicare enrollees
- ◆ Study Period 2011-2015
- ◆ CAP identified by ICD-9-CM

Study

population:

- ◆ Adult outpatients with CAP diagnosis and monotherapy antibiotic prescription claim within 3 days
- ◆ Antibiotics included amoxicillin, amoxicillin-clavulanate, ceftriaxone, azithromycin, clarithromycin, levofloxacin, moxifloxacin, ciprofloxacin, doxycycline

Patient population ascertainment from Truven Claims Database

Patient population	
Patients with CAP diagnosis with prescription claim within 3 days	890,784
Final sample size	413,801
Patients aged \geq 18 years old	251,947 (62.1%)

Frequency of initial antibiotic prescribing for CAP in Adults in USA 2011-2015

COHORT	Age 18 and Older		
	Frequency	Percent of Total	Percent of Therapeutic Class
TOTAL	257,165	100.0%	
Beta-lactam	16,749	6.5%	← 100.0%
amoxicillin	2,622	1.0%	15.7%
amoxicillin-clavulanate	13,904	5.4%	83.0%
ceftriaxone	223	0.1%	1.3%
Macrolide	112,054	43.6%	← 100.0%
azithromycin	101,492	39.5%	90.6%
clarithromycin	10,562	4.1%	9.4%
Fluoroquinolone	114,174	44.4%	← 100.0%
levofloxacin	95,019	36.9%	83.2%
moxifloxacin	14,160	5.5%	12.4%
ciprofloxacin	4,995	1.9%	4.4%
Tetracycline	14,188	5.5%	← 100.0%
doxycycline	14,188	5.5%	100.0%

Cipro and ceftriaxone were excluded from analysis due to small sample size.

Adverse Events of Special Interest (AESI) Stratified by age 18->65

Adverse Drug Events Among CABP Patients on Antibiotics - 18 and Above							
Adverse Drug Event	AGE STRATIFIED						P-Value
	18+ Total N= 251,947		18-64 Total N= 199,190		65+ Total N= 52,757		
	N	%	N	%	N	%	
Any Adverse Event	6,739	2.67%	4,623	2.32%	2,116	4.01%	<.0001
Cardiac	2,481	0.98%	1,726	0.87%	755	1.43%	<.0001
Hepatic	664	0.26%	470	0.24%	194	0.37%	<.0001
Liver failure	85	0.03%	59	0.03%	26	0.05%	0.0288
Musculo-skeletal	2,410	0.96%	1,743	0.88%	667	1.26%	<.0001
Tendonitis	2,410	0.96%	1,743	0.88%	667	1.26%	<.0001
Neuropathy	1,167	0.46%	719	0.36%	448	0.85%	<.0001
Peripheral neuropathy	756	0.30%	389	0.20%	367	0.70%	<.0001
Clostridium Difficile	179	0.07%	70	0.04%	109	0.21%	<.0001

AESI BY AGE GROUP BY DRUG CLASS (%)

AE	B-lactam	B-lactam	Macrolide	Macrolide	FQ	FQ	Tetracycline	Tetracycline
Age range yr	18-64	>65	18-64	>65	18-64	>65	18-64	>65
Any AE	2.38	4.1	2.01	3.66	2.66	5.25	2.39	3.88
Vent Tachy	0.23	0.77	0.11	0.19	0.14	0.69	0.15	0.76
Jaundice	0.06	0.1	0.03	0.02	0.05	0.07	0.06	0.06
LFTs increased	0.22	0.27	0.14	0.25	0.21	0.31	0.16	0.26
Liver failure	0.03	0.05	0.02	0.05	0.04	0.05	0.03	0.06
Tendonitis	0.86	1.00	0.77	1.17	1.01	1.41	0.83	0.93
Tendon rupture	0.06	0.1	0.07	0.13	0.1	0.16	0.09	0.09
<i>C difficile</i>	0.05	0.42	0.03	0.13	0.04	0.24	0.03	0.06
Neuritis	0.23	0.2	0.14	0.16	0.17	0.14	0.26	0.14
Peri Neur	0.2	0.92	0.16	0.6	0.24	0.74	0.19	0.6

Adverse Events in CAP aged >65 years

Adverse Drug Events Among CABP Patients on Antibiotics by Index Drug Class - Age 65 and Above											
Adverse Drug Event	INDEX DRUG CLASS STRATIFIED										P-Value
	Overall		Betalactam		Macrolide		Fluoroquinolone		Tetracycline		
	Total N**=		Total N**=		Total N**=		Total N**=		Total N**=		
	N	%	N	%	N	%	N	%	N	%	
Any Adverse Event	2,116	4.01%	165	4.11%	669	3.66%	1,149	4.25%	133	3.88%	0.0172
Cardiac	755	1.43%	56	1.40%	256	1.40%	384	1.42%	59	1.72%	0.5272
Ventricular tachycardia	369	0.70%	31	0.77%	126	0.69%	186	0.69%	26	0.76%	0.9046
Tachycardia	414	0.78%	29	0.72%	138	0.75%	213	0.79%	34	0.99%	0.5129
Hepatic	194	0.37%	14	0.35%	55	0.30%	112	0.41%	13	0.38%	0.2743
Jaundice	29	0.05%	4	0.10%	4	0.02%	19	0.07%	2	0.06%	0.0992
Elevated liver enzymes	150	0.28%	11	0.27%	46	0.25%	84	0.31%	9	0.26%	0.6993
Liver failure	26	0.05%	2	0.05%	9	0.05%	13	0.05%	2	0.06%	0.9956
Musculo-skeletal	667	1.26%	40	1.00%	214	1.17%	381	1.41%	32	0.93%	0.011
Tendonitis	667	1.26%	40	1.00%	214	1.17%	381	1.41%	32	0.93%	0.011
Tendon rupture	74	0.14%	4	0.10%	24	0.13%	43	0.16%	3	0.09%	0.5854
Neuropathy	448	0.85%	45	1.12%	138	0.75%	236	0.87%	29	0.85%	0.1289
Peripheral neuropathy	367	0.70%	37	0.92%	109	0.60%	200	0.74%	21	0.61%	0.0815
Neuritis	85	0.16%	8	0.20%	30	0.16%	39	0.14%	8	0.23%	0.5792
Clostridium Difficile	109	0.21%	17	0.42%	24	0.13%	66	0.24%	2	0.06%	0.0002

Key Findings: Fluoroquinolone and Macrolides Adverse Events of Special Interest in US Out Patients with CAP

	Macrolide	Fluoroquinolone	Odds Ratio
N of subjects	112,054	109,179	
Overall AE rate %	1.62	2.22	1.38 [1.30-1.46] p<0.0001
Vent Tachycardia%	0.21	0.27	1.33 [1.12-1.58] p<0.0001
Peripheral neuropathy%	0.18	0.33	1.79 [1.51-2.13] p<0.0001
Tendon rupture %	0.08	0.12	1.54 [1.30-1.82] p<0.0001
<i>C difficile</i> %	0.05	0.09	2.02 [1.44-2.82] p<0.0001

Study Limitations

- ◆ Although we have data on concomitant medications* we have not adjusted or accounted for them at this point.
- ◆ We have not presented these data by gender or other demographic, but we accept there may be some bias in reporting of events.

* Only patients on monotherapy were included.

Conclusions

- Adverse events due to antibiotics are common in adults treated for CAP.
- This is a “snapshot” of AESI as noted by regulators and does not include the more common expected events such as nausea, diarrhea, vomiting etc.
- AEs occur more often in the older patient (>65)
- Significant and serious AEs were observed with all classes. In a head to head comparison fluoroquinolones had more AESI’s than macrolides.
- BUT B-lactams are not without some issues (e.g. *C.difficile*).
- Consideration of AE risk potential should be a priority for physicians managing adult outpatients with CAP.