Prescribing pattern of empirical antibiotics in the hospital-acquired pneumonia using OMOP-CDM

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Introduction

- Hospital-acquired pneumonia (HAP) is one of the most common healthcare-associated infections (HAIs).
- Appropriate use of antibiotics is critical for suppressing microbial antibiotic resistance.
- Surveillance of HAIs including HAP is very time- and resource-intensive, as it usually relies on manual chart review.

Objectives

- The aim of this study is to define appropriate phenotype (phenotyping) and to assess of empirical antibiotics use in HAP population (treatment pathway) to find unmet needs in clinical settings.
- This study is a preliminary study for the prediction study of appropriate antibiotics selection.

Method

Phenotyping

Use ATLAS

Data source

Electronic medical records of AUSOM database from 1996 to 2018

Treatment pathway

Applying prior OHDSI study

Characterizing treatment pathways at scale using the OHDSI network

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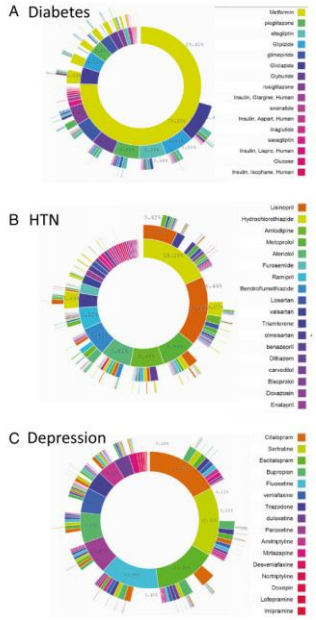


OHDSI

AJOU UNIVERSITY 1973

SEOUL NATIONAL UNIVERSITY 1946

Method

Initial cohort entry

- Inpatient visit > 7 days (index date)
- Age ≥ 18

Inclusion criteria

- No pneumonia diagnosis between day 0 – day 2
- No antibiotics prescription between day 0 – day 2
- No other infection during inpatient stay
- At least 1 pneumonia diagnosis between day 3 – visit end date

Method

Only 9 patients who matched the criteria

		Match Rate	Matches	Total Events
	Summary Statistics:	0.01%	9	137,082

Inclusion Rule	N	% Remain	% Diff
1. No pneumonia	128,610	93.82%	6.18%
2. No anti first 2 days	94,113	68.65%	25.17%
3. No other infection	92,748	67.65%	1.00%
4. Pneumonia after day 3	9	0.01%	67.65%

Why?

- Hospital-acquired pneumonia is difficult to diagnose if the clinical characteristics are ambiguous because symptoms are non-specific.
- Many physicians do not input the code-based diagnosis into the EMR system, but only write symptoms and suspected diagnosis to progress notes.
- This suggests that surrogate criteria are needed.

Method

Initial cohort entry

- Inpatient visit > 7 days (index date)
- Age ≥ 18

Inclusion criteria

- No pneumonia diagnosis between day 0 – day 2
- No antibiotics prescription between day 0 – day 2
- No other infection during inpatient stay

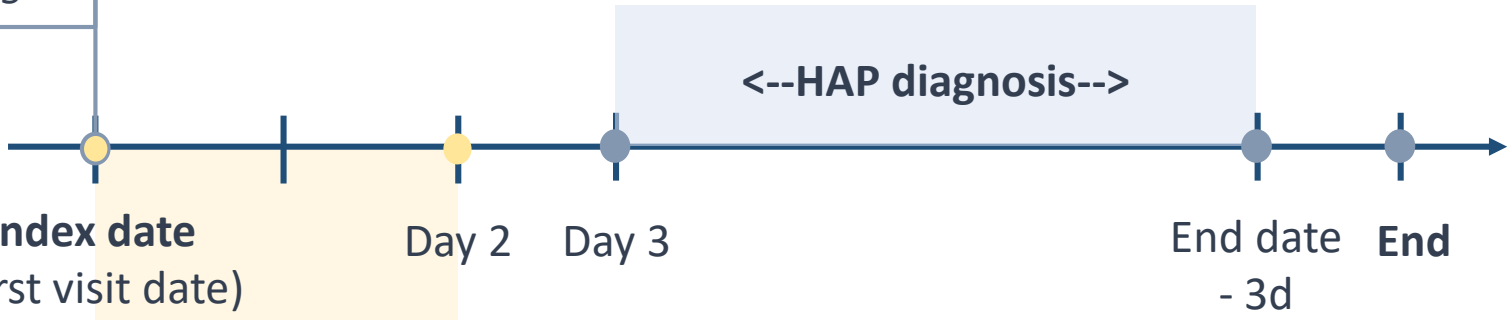
Surrogate criteria for HAP

- At least 1 occurrence of Chest CT / Chest X-ray between index date + 3 days and cohort end date – 3 days with order of antibiotics and culture test
- No other diagnosis of disease related with Chest CT / Chest X ray (e.g. COPD, TB, HF, Lung ca, H.Pylori, Gastritis) during inpatient stay
- At least 1 keyword occurrence in specific clinical note
  - Specific note: Progress note, discharge note, consultation request / answer note
  - Specific Keyword: “Pneumonia”, “Hospital acquired pneumonia”, “HAP”, “Consolidation”, “폐렴(Pneumonia as Korean)”, “병원성 폐렴(Hospital acquired pneumonia as Korean)”

Method

- ***At least 1 pneumonia diagnosis between day 3 – visit end date***

Initial cohort entry
- IP visit > 7d
- Age ≥ 18 yrs



<--Exclude CAP-->
- No pneumonia
- No antibiotics
- No specific keyword*

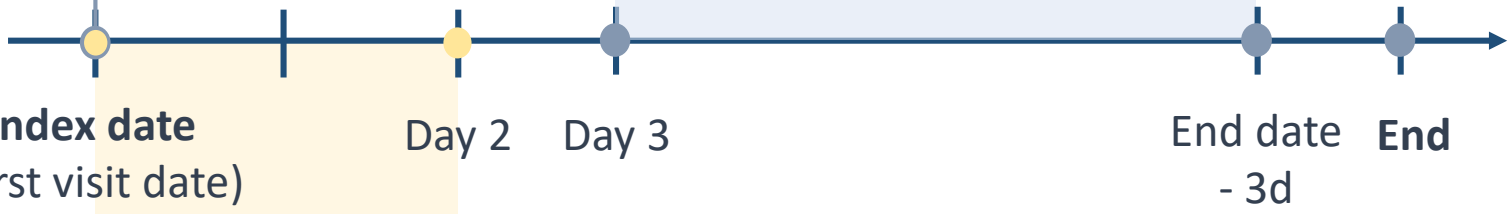
*Specific Keyword:
"Pneumonia", "Hospital acquired pneumonia", "HAP", "Consolidation", "폐렴", "병원성 폐렴"

<----------No other infections during inpatient stay---------->

Method

Initial cohort entry
- IP visit > 7d
- Age ≥ 18 yrs

- *At least 1 pneumonia diagnosis between day 3 – visit end date*
- (Chest CT OR Chest X-ray) with (Abx AND Culture test)
- No COPD, TB, HF, Lung ca, Gastritis
- Specific Keyword* in clinical note



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- No antibiotics
- No specific keyword*

**Specific Keyword:*
"Pneumonia", "Hospital acquired pneumonia", "HAP", "Consolidation", "폐렴", "병원성 폐렴"

**Specific note:*
Progress note, discharge note, consultation note

<----------No other infections during inpatient stay---------->

Method

Drug exposure

- The target antibiotics were selected based on the 2016 IDSA/ATS HAP guidelines and 2007 CAP guidelines.
- 42 ingredients of antibiotic drugs
- Exclude the topical, ophthalmic formulations

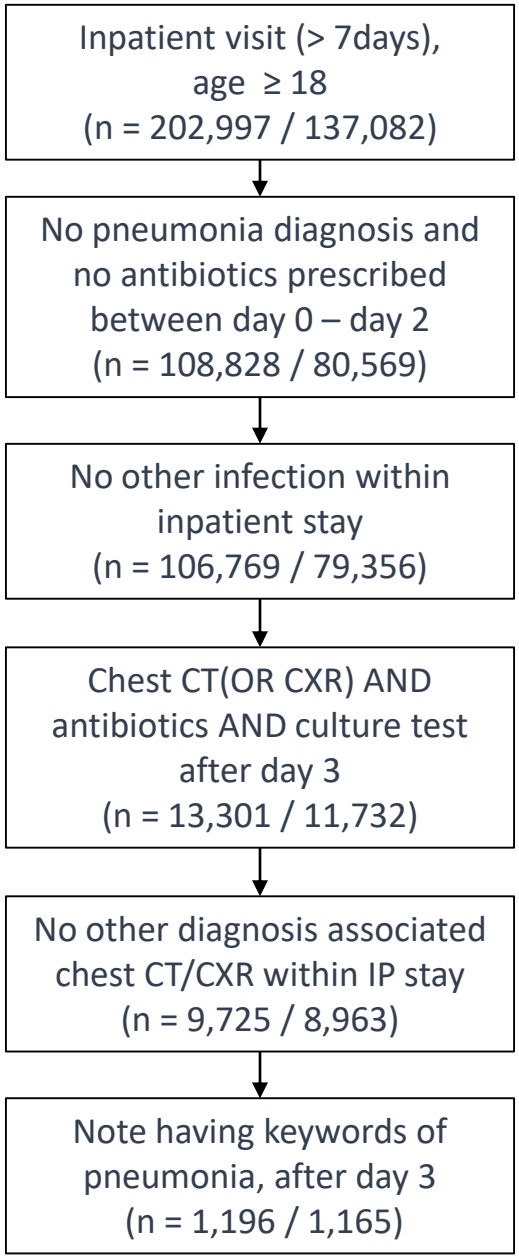
Method

Treatment pathway

- We Modified the SQL query from *Hripsack et al. PNAS 2016* https://github.com/OHDSI/StudyProtocols/tree/master/TxPathways12mo

- Antibiotics are prescribed every day during an inpatient stay.
- In the case of "combination", it is defined as cases where drugs are overlapped for more than 2 days.
- We focused on the initial empirical antibiotic therapy.

Results


Inpatient visit (> 7days), age ≥ 18 (n = 202,997 / 137,082)
No pneumonia diagnosis and no antibiotics prescribed between day 0 – day 2 (n = 108,828 / 80,569)
No other infection within inpatient stay (n = 106,769 / 79,356)
Chest CT(OR CXR) AND antibiotics AND culture test after day 3 (n = 13,301 / 11,732)
No other diagnosis associated chest CT/CXR within IP stay (n = 9,725 / 8,963)
Note having keywords of pneumonia, after day 3 (n = 1,196 / 1,165)

Results

AUSOM HAP cohort			
Number of events (n)		**To first antibiotics from index (days)**	
Cohort events	1,196	- Min	3
No of patients	1,165	- Max	105
No of events in pathway	1,196	- Mean ± SD	8 ± 8.09
No of pathway	637 (when minimum combo days = 2d)	- Median (IQR)	6 (4, 11)
Length of stay (days)		**Number of prescriptions**	
- Min	8	- Min	1
- Max	326	- Max	220
- Mean ± SD	37 ± 30.00	- Mean ± SD	29 ± 29.30
- Median (IQR)	29 (18, 48)	- Median (IQR)	20 (11, 36)

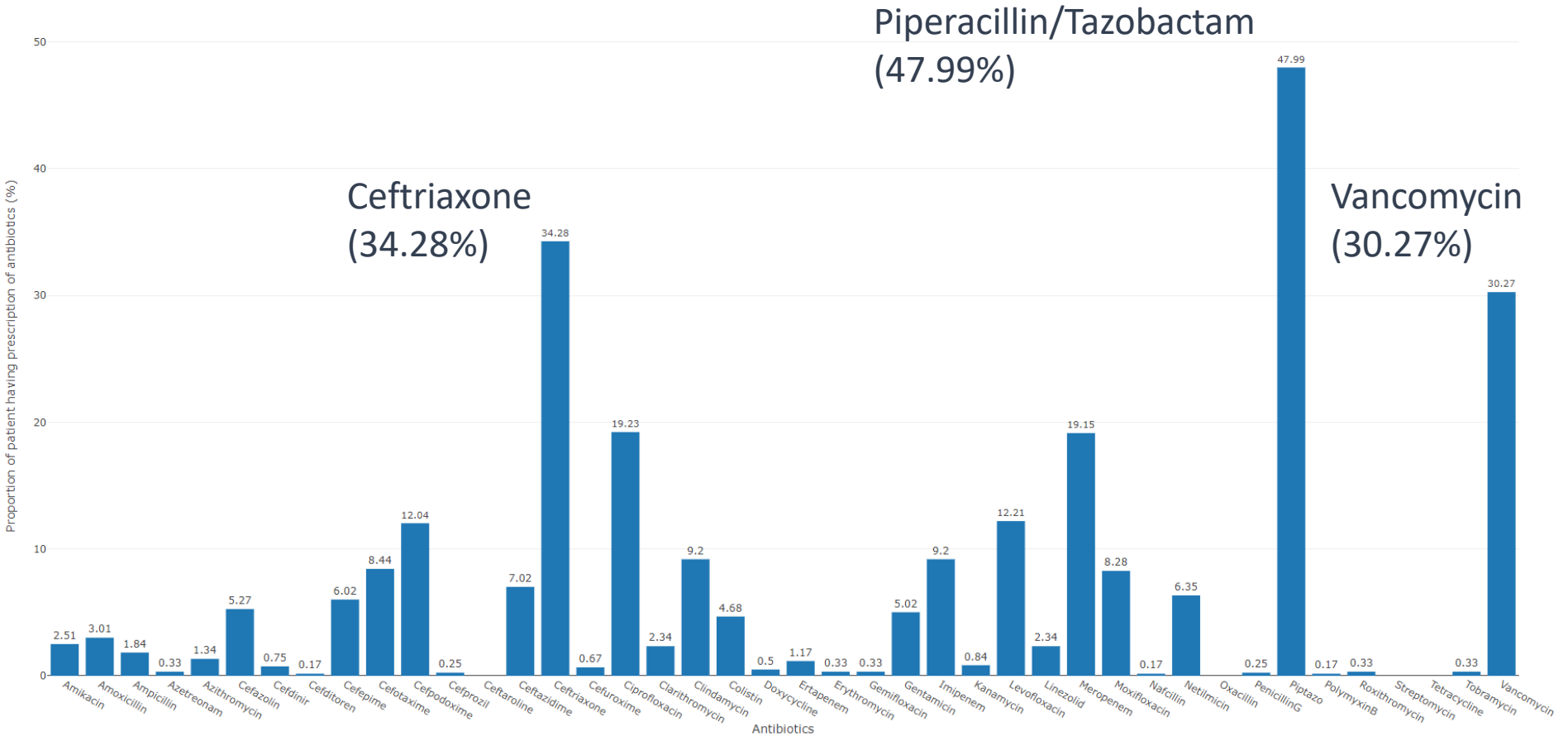
Results

Table 1. Total prescription rate of antibiotics in inpatient stay of HAP population.

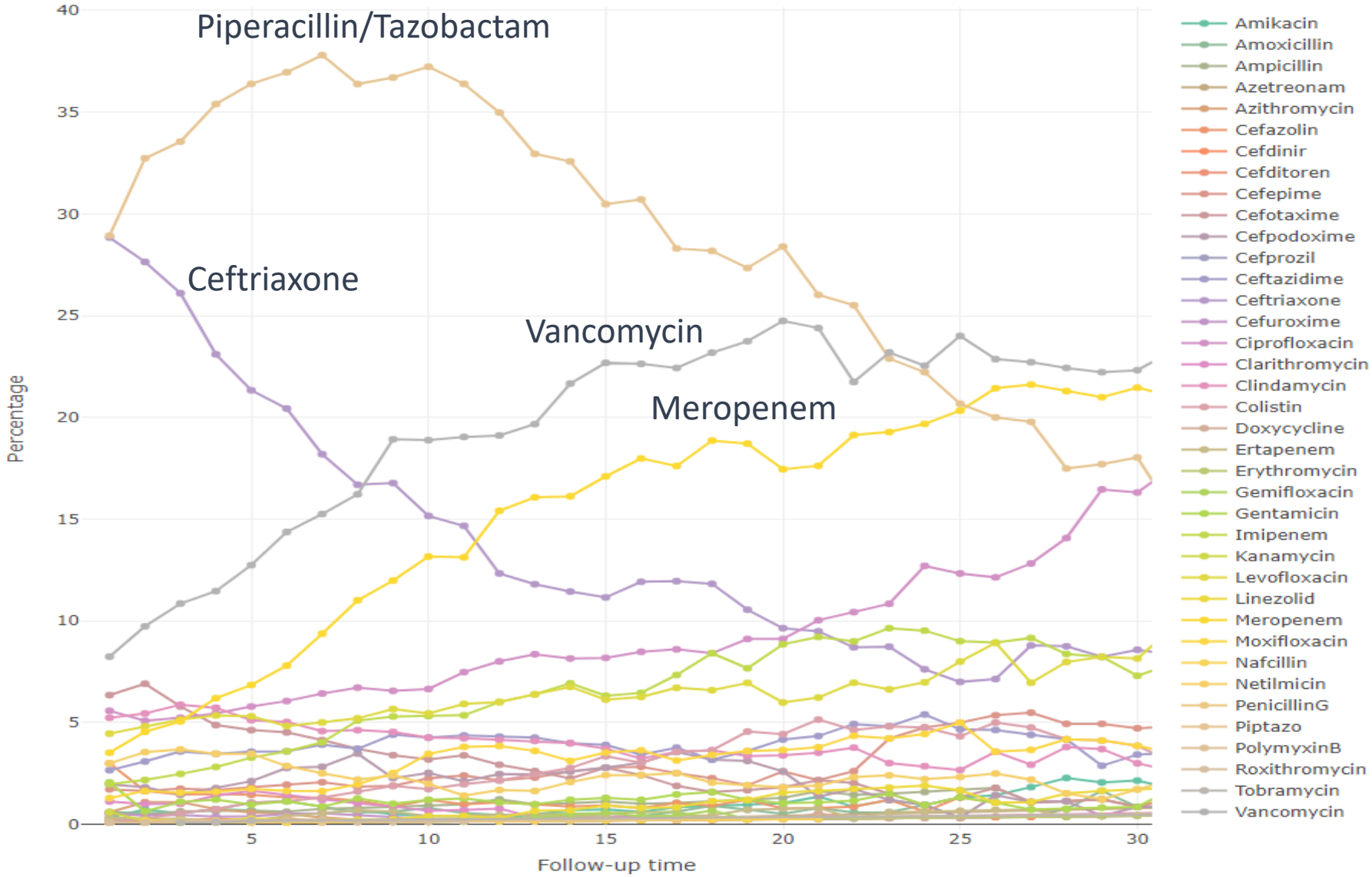
Drug name	Number of prescriptions	n (%)*
Piperacillin/Tazobactam	6,667	574 (47.99%)
Ceftriaxone	3,657	410 (34.28%)
Vancomycin	5,074	362 (30.27%)
Ciprofloxacin	2,412	230 (19.23%)
Meropenem	3,696	229 (19.15%)
Levofloxacin	1,786	146 (12.21%)
Cefpodoxime	577	144 (12.04%)
Imipenem	1,559	110 (9.2%)
Clindamycin	1,059	110 (9.2%)
Cefotaxime	749	101 (8.44%)
Moxifloxacin	751	99 (8.28%)
Ceftazidime	1,042	84 (7.02%)
Netilmicin	628	76 (6.35%)
Cefepime	833	72 (6.02%)
Cefazolin	282	63 (5.27%)
Gentamicin	292	60 (5.02%)

* Antibiotics prescribed over the 5% of the total number of prescriptions.

Antibiotics use during overall in-hospital stay



Antibiotics use for 30 days after first prescription



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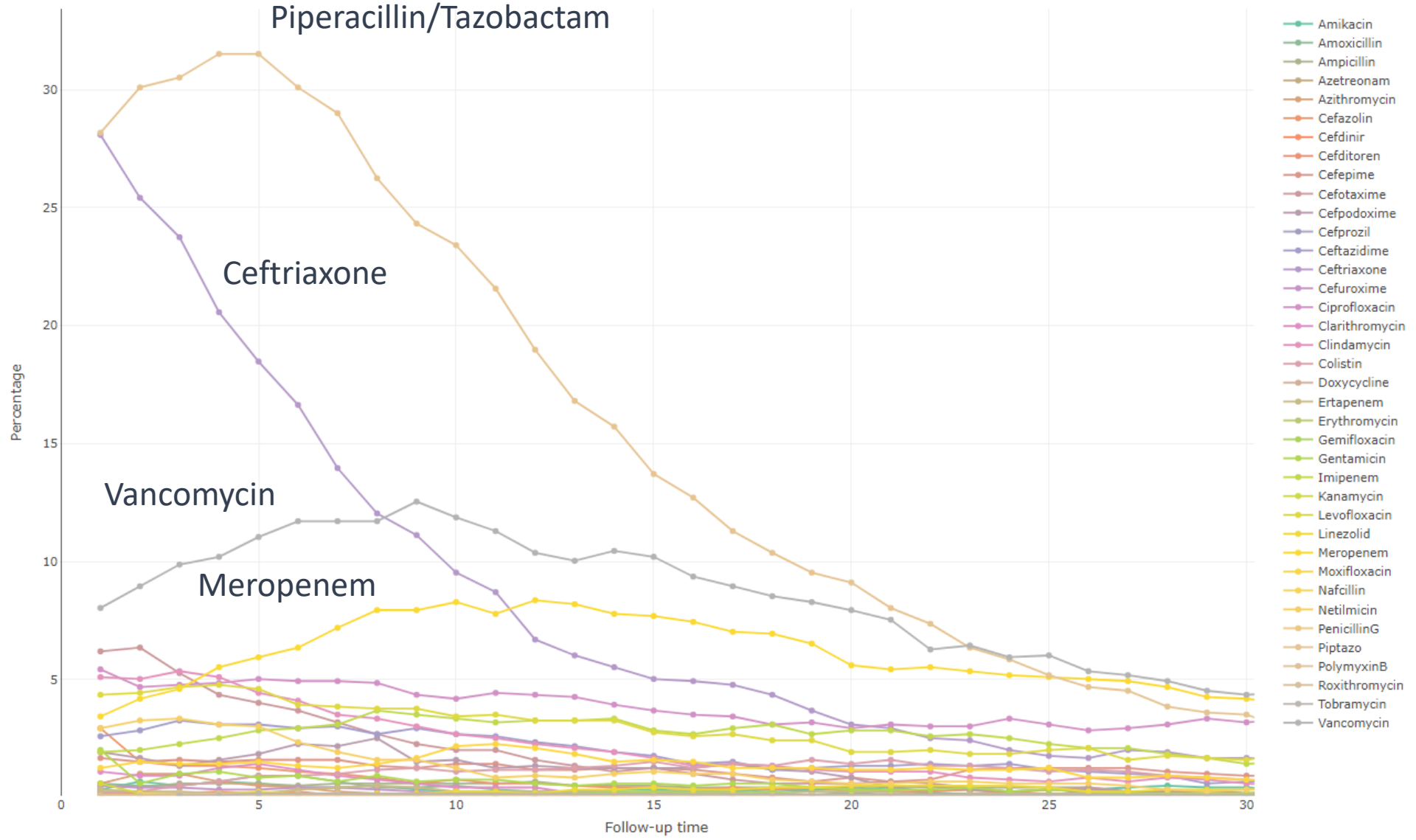
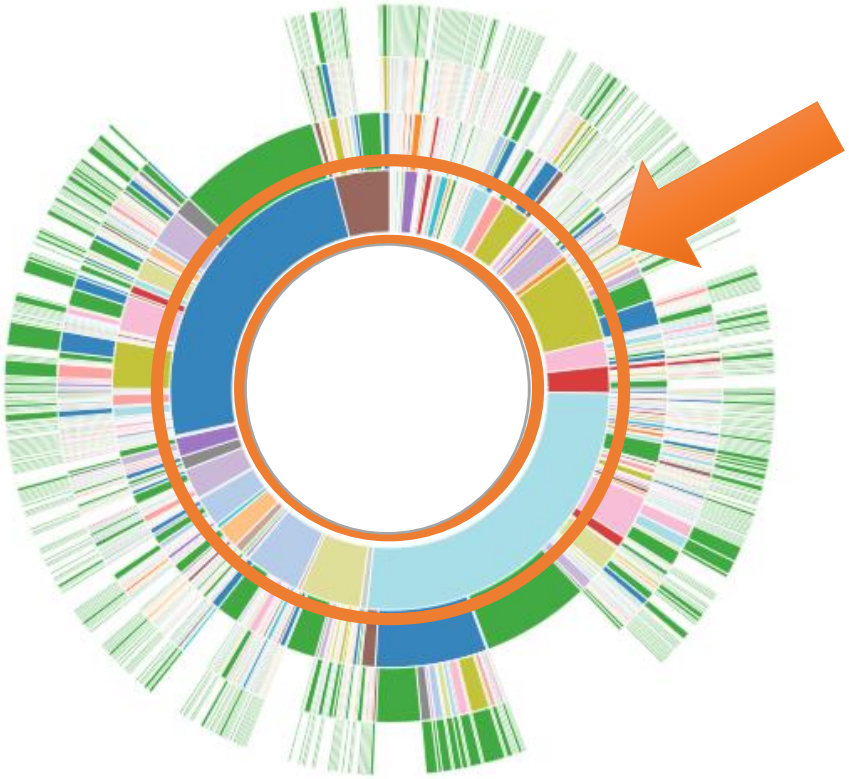


Prescribing pattern of antibiotics for patients in the HAP cohort

AUSOM HAP cohort
(Case = 1,196)

AUSOM (case = 1,196)		
1st choice of empirical antibiotics therapy	**N**	**Percent (%)**
Ceftriaxone	**316**	**26.42**
Piperacillin/tazobactam	**290**	**24.25**
Cefotaxime	75	6.27
Ciprofloxacin	54	4.52
Clindamycin	50	4.18
Vancomycin	49	4.10
Levofloxacin	27	2.26
Meropenem	27	2.26
Piperacillin/tazobactam, Vancomycin	25	2.09
Ceftazidime	24	2.01
Cefazolin	23	1.92
Cefpodoxime	23	1.92
Imipenem/Cilastatin	20	1.67
Netilmicin	17	1.42
Levofloxacin, Piperacillin/tazobactam	16	1.34
Meropenem, Vancomycin	13	1.09
Cefepime, Netilmicin	12	1.00
Moxifloxacin	12	1.00
Gentamicin	8	0.67
Ceftriaxone, Clindamycin	7	0.59

The 1st choices of empirical antibiotics



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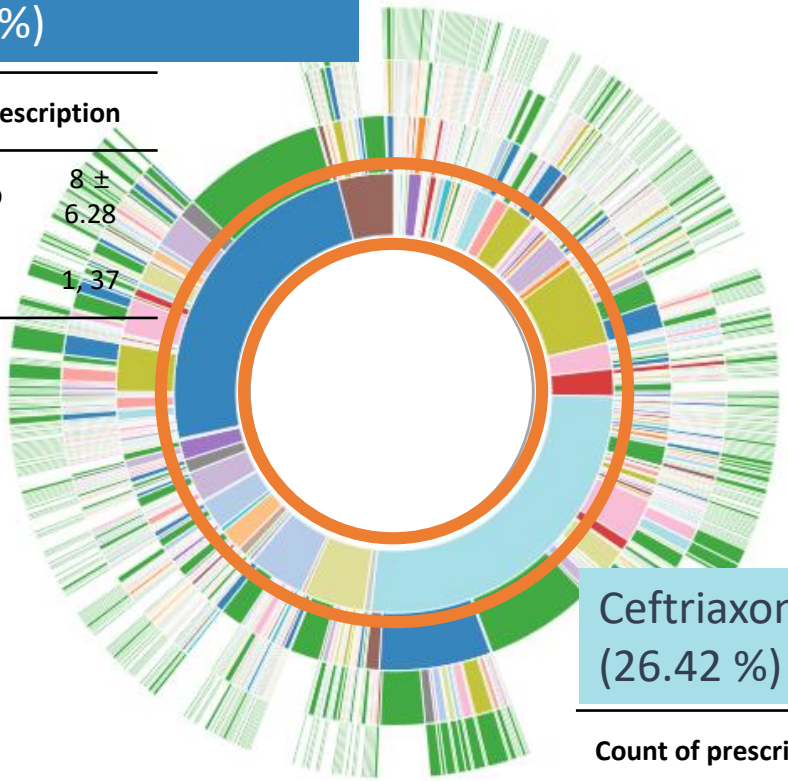
The 1st choices of empirical antibiotics

Piperacillin/Tazobactam (24.25 %)

Count of prescription	
Mean ± SD	8 ± 6.28
Min, Max	1, 37



Ceftriaxone (26.42 %)

Count of prescription	
Mean ± SD	7 ± 6.51
Min, Max	1, 47

AUSOM HAP cohort (Case = 1,196)

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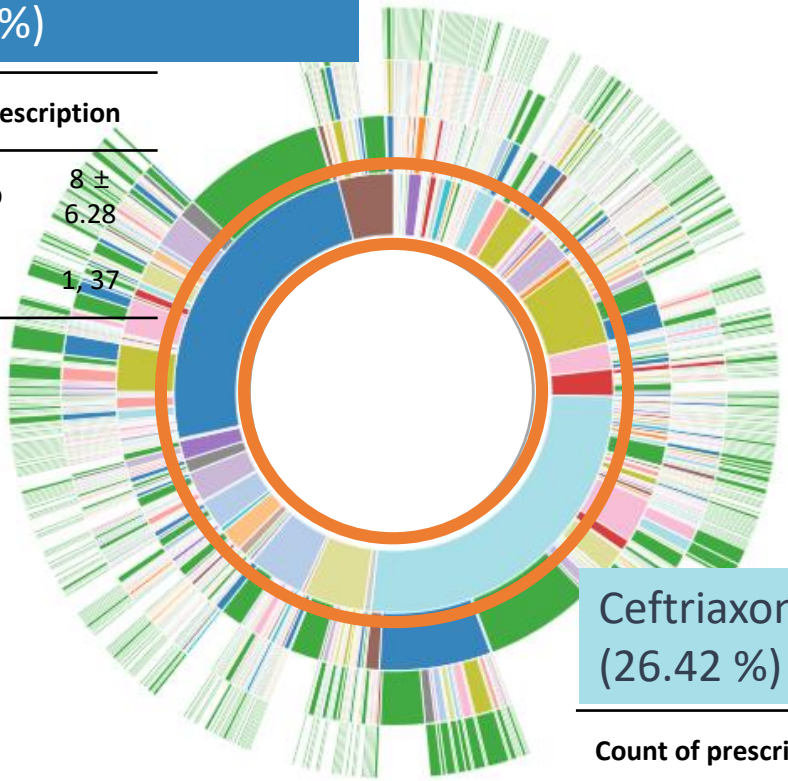

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Moxifloxacin	12	1.00
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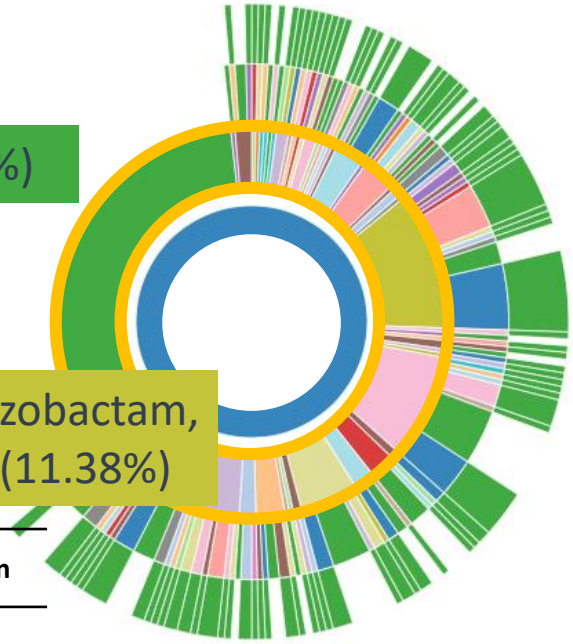
Antibiotic changes after the firstly selected *piperacillin/tazobactam*

Pip/tazo as first line
(Case = 290)

Piperacillin/Tazobactam use as a first choice (case = 290)		
Next choice	**n**	**Percent (%)**
ends	**100**	**34.48**
Piperacillin/tazobactam, Vancomycin	**33**	**11.38**
Cefpodoxime	25	8.62
Meropenem	24	8.28
Ciprofloxacin	14	4.83
Moxifloxacin	13	4.48
Meropenem, Vancomycin	8	2.76
Levofloxacin, Piperacillin/tazobactam	7	2.41
Imipenem/Cilastatin	7	2.41
Ceftazidime	6	2.07

Antibiotic changes after the firstly selected *piperacillin/tazobactam*



Count of prescription	
Mean ± SD	5 ± 4.89
Min, Max	1, 23

Pip/tazo as first line (Case = 290)

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Next choice	n	Percent (%)
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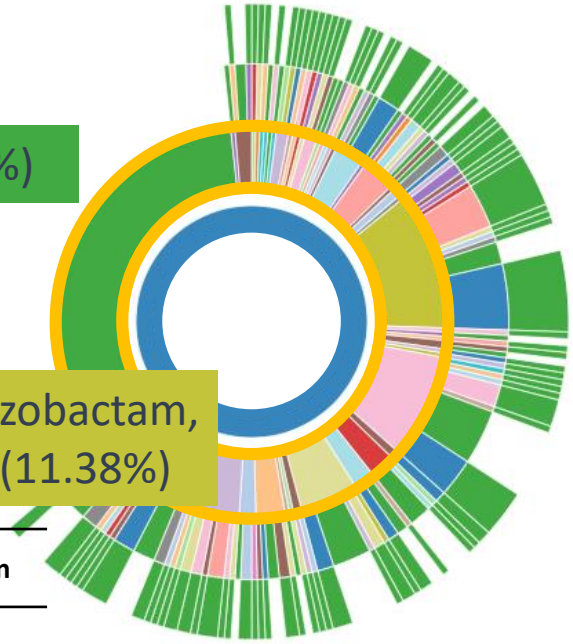

Count of prescription	
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Min, Max	1, 23

Pip/tazo as first line
(Case = 290)

Pip/tazo mono→ Pip/tazo combi (18.92%)

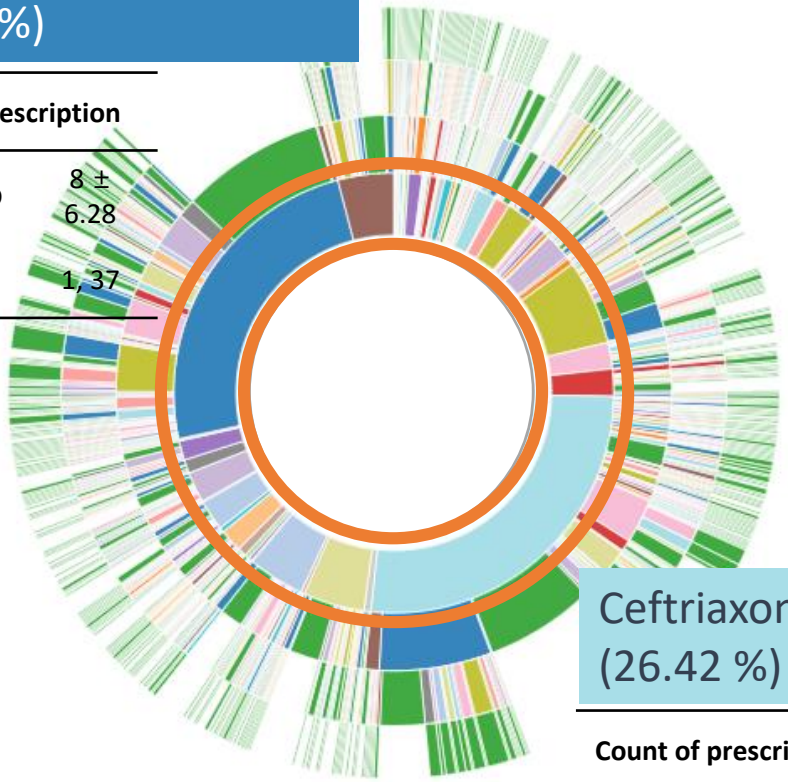
Piperacillin/Tazobactam use as a first choice (case = 290)

Next choice	n	Percent (%)
Piperacillin/tazobactam, Vancomycin	33	11.38
Levofloxacin, Piperacillin/tazobactam	7	2.41
Ciprofloxacin, Piperacillin/tazobactam	3	1.03
Colistin, Piperacillin/tazobactam	3	1.03
moxifloxacin, Piperacillin/tazobactam	2	0.69
Azithromycin, Piperacillin/tazobactam	1	0.34
Ciprofloxacin, Piperacillin/tazobactam, Vancomycin	1	0.34
Colistin, Piperacillin/tazobactam, Vancomycin	1	0.34
Gentamicin, Piperacillin/tazobactam	1	0.34
Imipenem/Cilastatin, Piperacillin/tazobactam	1	0.34
linezolid, Piperacillin/tazobactam	1	0.34
Piperacillin/tazobactam, cefpodoxime	1	0.34
Total	**55**	**18.92**

The 1st choices of empirical antibiotics

Piperacillin/Tazobactam (24.25 %)

Count of prescription	
Mean ± SD	8 ± 6.28
Min, Max	1, 37



Ceftriaxone (26.42 %)

Count of prescription	
Mean ± SD	7 ± 6.51
Min, Max	1, 47

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Ceftriaxone, Clindamycin	7	0.59

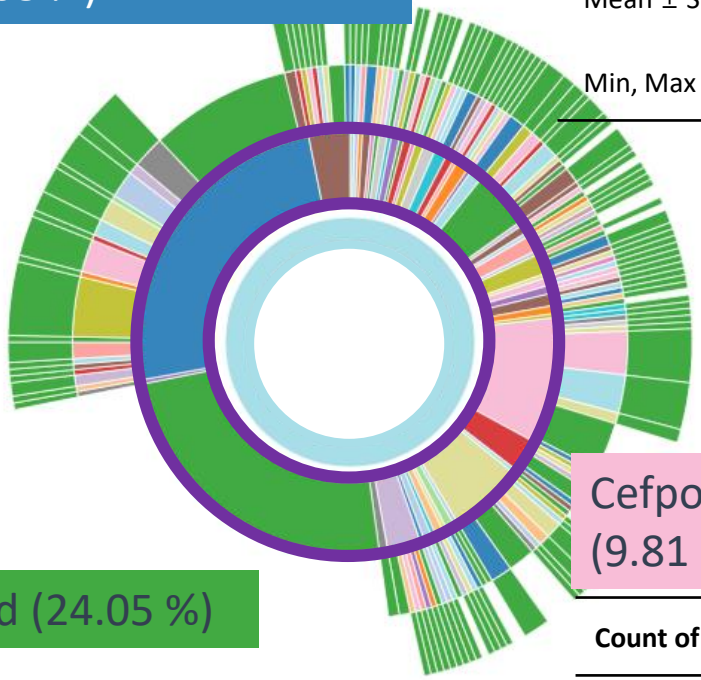
Antibiotic changes after the firstly selected *ceftriaxone*

Ceftriaxone as first line
(Case = 316)

Ceftriaxone use as a first choice (case = 316)		
Next choice	**n**	**Percent (%)**
Piperacillin/tazobactam	**78**	**24.68**
ends	**76**	**24.05**
Cefpodoxime	31	9.81
Ciprofloxacin	18	5.7
Ceftriaxone, Vancomycin	14	4.43
Vancomycin	10	3.16
Ceftazidime	8	2.53
Meropenem	8	2.53
Piperacillin/tazobactam, Vancomycin	5	1.58
meropenem, Vancomycin	4	1.27

Antibiotic changes after the firstly selected ceftriaxone

Piperacillin/Tazobactam (24.68 %)



Cefpodoxime (9.81 %)

End (24.05 %)

Ceftriaxone as first line (Case = 316)

Count of prescription	
Mean ± SD	7 ± 5.59
Min, Max	1, 27

Count of prescription	
Mean ± SD	3 ± 5.59
Min, Max	1, 30

Ceftriaxone use as a first choice (case = 316)

Next choice	n	Percent (%)
Piperacillin/tazobactam	**78**	**24.68**
ends	**76**	**24.05**
Cefpodoxime	31	9.81
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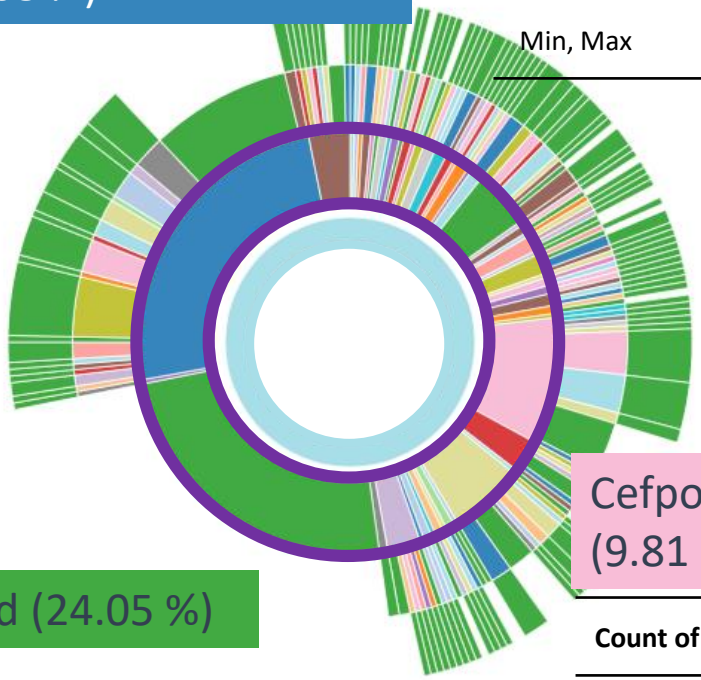

Cefpodoxime (9.81 %)

End (24.05 %)

Count of prescription	
Mean ± SD	3 ± 5.59
Min, Max	1, 30

Ceftriaxone as first line (Case = 316)

Ceftriaxone → Pip/tazo or Vancomycin (38.6 %)

Ceftriaxone use as a first choice (case = 316)		
Next choice	**n**	**Percent (%)**
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meropenem, Vancomycin	4	1.27
Ceftriaxone, Piperacillin/tazobactam	3	0.95
Amikacin, Piperacillin/tazobactam	2	0.63
Imipenem/Cilastatin, Vancomycin	2	0.63
Clindamycin, Piperacillin/tazobactam, Vancomycin	1	0.32
Levofloxacin, Piperacillin/tazobactam	1	0.32
moxifloxacin, Piperacillin/tazobactam	1	0.32
Amikacin, meropenem, Vancomycin	1	0.32
total	**122**	**38.61**

Discussion

- Infectious diseases are considered acute and require short term treatments for about a week to two weeks. So the early treatment decision with an empirical treatment is critical for prognosis and resistant prevention.
- HAP cohort definition using ICD-10 code showed low positive predictive value and sensitivity in the prior literatures[1)].
- We identified that the surrogate criteria of hospital acquired pneumonia for the cohort definition are needed.
- Therefore, we defined the extracting algorithm for hospital-acquired pneumonia using OMOP-CDM.

1) Wolfensberger A, Meier AH, Kuster SP, et al. Should International Classification of Diseases codes be used to survey hospital-acquired pneumonia? *J Hosp Infect* 2018;99(1):81-84.

Discussion

- According to the IDSA guidelines, it is recommended to use antibiotics having pseudomonas coverage as a first choice for hospital-acquired pneumonia treatment.
- In our study, Ceftriaxone was used in 26 % of HAP patients as the first choice, and most of them changed to drugs covering pseudomonas.
- The clinical hurdle to the use of appropriate antibiotics is that there is no clear diagnostic method for hospital-acquired pneumonia. (we can consider the development of prediction tool.)
- However, it seems necessary to reduce the average duration of broad-spectrum antibiotics (e.g. Ceftriaxone) use with a more aggressive antimicrobial stewardship program in HAP patients.

Discussion

Not at High Risk of Mortality[a] and no Factors Increasing the Likelihood of MRSA[b,c]	Not at High Risk of Mortality[a] but With Factors Increasing the Likelihood of MRSA[b,c]	High Risk of Mortality or Receipt of Intravenous Antibiotics During the Prior 90 d[a,c]
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h
OR	OR	OR
Cefepime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily
	Ciprofloxacin 400 mg IV q8h	Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h
Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h
	OR	OR
	Aztreonam 2 g IV q8h	Amikacin 15–20 mg/kg IV daily
		Gentamicin 5–7 mg/kg IV daily
		Tobramycin 5–7 mg/kg IV daily
		OR
		Aztreonam[e] 2 g IV q8h
	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Plus: Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg IV × 1 for severe illness)
	OR	OR
	Linezolid 600 mg IV q12h	Linezolid 600 mg IV q12h
		If MRSA coverage is not going to be used, include coverage for MSSA. Options include: Piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.
If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam–based antibiotic, include coverage for MSSA.		

Limitation

- There is no validation for defined HAP cohort using surrogate criteria. (we want to know the situation of other sites)

- There is no microbiology culture and sensitivity results available yet in CDM.

Thank you

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