Is empiric antipseudomonal therapy needed in culture-negative hospital-acquired pneumonia?

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NHG Health

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Background & Objectives

- Hospital-acquired pneumonia (HAP), and its subset ventilator-associated pneumonia (VAP), is a common nosocomial infection, associated with high medical costs, morbidity and mortality.[1, 2]
- Current guidelines recommend the empiric coverage of *Pseudomonas aeruginosa* in HAP[3] but there is limited guidance on de-escalation strategies after clinical improvement is observed and multidrug resistant organisms (MDRO) are not isolated.[3, 4]
- In Tan Tock Seng Hospital (TTSH) Singapore, intravenous (IV) piperacillin-tazobactam (PIP) is commonly initiated for HAP. Clinicians then de-escalate antibiotics to oral amoxicillin-clavulanate (AUG) with or without ciprofloxacin (CIP).
- CIP is a useful oral agent for *P. aeruginosa* and reducing use of CIP is vital to preserve its role in the antimicrobial armamentarium.
- This study aimed to compare the efficacy and safety of adjunct oral CIP to oral AUG in step-down therapy for culture-negative HAP.

Methods

- **Type of Study:** Retrospective cohort study
- **Period of Review:** August 2022 – January 2023
- **Inclusion Criteria:** Patients aged ≥ 21 years started on PIP for ≥ 2 days for culture-negative HAP* & oralised to AUG ± CIP for ≥ 2 days
  - ➢ Only first episodes of HAP during study period were included
  - ➢ Patients with concurrent infections were excluded

*HAP was defined as presence of new or progressive lung infiltrate and clinical evidence suggestive of pneumonia i.e. new onset of fever, purulent sputum, leucocytosis, and decline in oxygenation) acquired > 48 hours of admission and not incubating at time of admission.[3]

- ➢ Patients would be classified as having a VAP if they fulfilled the criteria of HAP and had acquired the pneumonia > 48 hours after intubation.

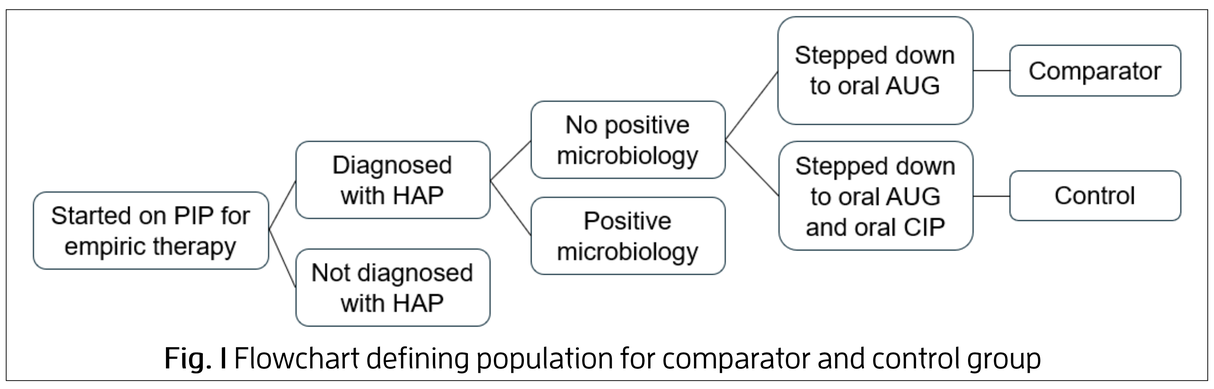

Fig. 1 Flowchart defining population for comparator and control group

- **Primary outcome:** 30-day all-cause mortality from start of PIP
- **Secondary outcomes:** (a) Clinical cure at end of oral therapy – survival with improvement or resolution of symptoms without new antibiotics initiated; (b) 30-day pneumonia recurrence - clinical symptoms and new or progressive lung infiltrates within 30 days of completing oral therapy; (c) adverse events from start of oral therapy until 14 days after completion; (d) 30-day MDRO# acquisition rate

#MDROs: Organisms resistant to agents in ≥3 classes of antimicrobials where susceptibility is expected.[5] Examples include methicillin-resistant *Staphylococcus aureus*, multidrug-resistant *Pseudomonas*, multidrug-resistant *Acinetobacter*, and vancomycin-resistant *Enterococcus*

- **Statistical Analysis:**
  - ➢ Continuous data: Two-sided independent samples t-test or Mann-Whitney U test
    - Tests for normality : Shapiro-Wilk or Kolmogorov-Smirov test
  - ➢ Categorical data: Chi-squared test or Fisher's exact test
  - ➢ Multivariate logistic regression analysis conducted identify independent risk factors for 30-day mortality
    - Variables with $p < 0.5$ in the univariate analysis and CIP use were added into the model
  - ➢ Post-hoc multivariate analysis performed for clinical cure
    - Variables with $p < 0.5$ in the univariate analysis and CIP use were included

Results

- 175 patients were included - 104 patients oralised to AUG alone; 71 patients oralised to AUG with adjunct CIP.
- 30-day mortality was not significantly different between both groups (see Table 2) and oral AUG monotherapy was not associated with increased 30-day mortality in multivariate analysis (see Table 3).

Results

- Charlson's Comorbidity Index (CCI) was associated with an increased risk of 30-day mortality (see Table 3)
- Secondary outcomes were similar between both groups (see Table 2).

Table 1. Characteristics of patients classified based on oral therapy in culture-negative HAP

Characteristic	Oral AUG & CIP (n=71)[a]	Oral AUG (n=104)[a]	p-value[b]
Age	82.00 (72.00 – 88.00)	79.00 (67.25 – 84.00)	NS
Male	42 (59.15)	60 (57.69)	NS
Chinese	61 (85.92)	88 (84.62)	NS
Chronic obstructive pulmonary disease (COPD)	9 (12.68)	9 (8.65)	NS
Bronchiectasis	6 (8.45)	3 (2.89)	NS
Structural lung disease	1 (1.41)	4 (3.85)	NS
VAP	1 (1.41)	6 (5.77)	NS
Late-onset	60 (84.51)	72 (69.23)	**<0.05**
Admission to intensive care unit	0 (0)	9 (8.65)	**<0.05**
Complicated pneumonia	6 (8.45)	20 (19.23)	**<0.05**
Use of IV antimicrobials within past 90 days	54 (76.06)	69 (66.35)	NS
CCI	6.00 (5.00 – 7.00)	7.00 (5.00 – 8.00)	NS
Total days of IV antibiotics	4.00 (3.00 – 5.00)	3.00 (3.00 – 5.00)	NS
Total days of antibiotics	8.00 (7.00 – 8.00)	7.00 (7.00 – 8.00)	NS
APACHE II score at initiation of IV antibiotics	11.00 (9.00 – 14.00)	12.00 (9.25 – 15.00)	NS
APACHE II score at initiation of oral antibiotic	10.00 (8.00 – 13.00)	11.00 (8.00 – 14.00)	NS

[a]Expressed as either median (interquartile range) or number (%)
[b]NS denotes non-significance

Table 2. Comparison of efficacy and safety outcomes between patients who received oral AUG monotherapy and oral AUG with adjunct CIP for culture-negative HAP

Outcome	Oral AUG & CIP (n=71)[a]	Oral AUG (n=104)[a]	p-value
Mortality	9 (12.67)	13 (12.50)	0.97
Clinical cure	58 (81.69)	87 (83.65)	0.74
Recurrence	19 (26.76)	21 (20.19)	0.31
Adverse events	4 (5.63)	10 (9.62)	0.34
Clostridioides difficile associated diarrhoea	0 (0)	1 (0.96)	>0.99
Diarrhoea	4 (5.63)	5 (4.81)	>0.99
Oropharyngeal candidiasis	0 (0)	2 (1.92)	0.52
Nausea/Vomiting	0 (0)	2 (1.92)	0.52
MDRO acquisition	3 (4.23)	3 (2.88)	0.69

[a]Expressed as number (%)

Table 3. Univariate and multivariate analysis of 30-day mortality in patients who received oral AUG monotherapy for culture-negative HAP

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	**p-value**	**Adjusted odds ratio (95% confidence interval)**	**p-value**
AUG monotherapy	0.98 (0.40 – 2.44)	0.97	0.92 (0.34 – 2.49)	0.86
Age	1.01 (0.98 – 1.05)	0.48	0.99 (0.95 – 1.04)	0.80
Chinese	1.86 (0.41 – 8.49)	0.42	1.46 (0.29 – 7.33)	0.64
Complicated pneumonia	1.85 (0.62 – 5.55)	0.27	1.44 (0.44 – 4.72)	0.54
COPD	2.21 (0.66 – 7.44)	0.20	2.27 (0.58 – 8.87)	0.24
Bronchiectasis	2.09 (0.41 – 10.75)	0.38	2.01 (0.34 – 12.00)	0.44
Late-onset	1.54 (0.49 – 4.83)	0.46	1.77 (0.52 – 6.06)	0.36
Use of IV antimicrobials within past 90 days	0.71 (0.28 – 1.80)	0.47	0.67 (0.25 – 1.79)	0.42
CCI	1.28 (1.06 – 1.55)	**0.01**	1.32 (1.06 – 1.63)	**0.01**

- In post-hoc multivariate analysis, oral AUG monotherapy was not associated with decreased clinical cure rates - adjusted odds ratio 1.15 (95% confidence interval: 0.49 – 2.71)

Conclusion

- Oral AUG monotherapy was not associated with increased 30-day mortality. However, this study was underpowered to detect mortality differences. There is also limited applicability to patients with COPD, bronchiectasis and other structural lung diseases due to small numbers included.
- Larger prospective studies are required to evaluate efficacy and safety of removing antipseudomonal coverage in oral therapy for culture-negative HAP.

References

(1) Kalesar I, et al. *CHEST.* 2010;138(4):739A. (2) Jones BE, et al. *JAMA Netw Open.* 2023;6(5):e2314185. (3) Kalil et al. *Clin Infect Dis.* 2016;63(5):e61-e111. (4) Song JU, et al. *Korean J Intern Med.* 2023;28(5):704-713. (5) Magiorakos AP, et al. *Clin Microbiol Infect.* 2012;18(3):268-281.