Antibiotic Management Practices in Patients with Viral Respiratory Infections: A Retrospective Cohort Study

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Abstract

Objectives
To identify patient characteristics associated with physicians' decision to continue empiric antibiotics in patients with a lower respiratory tract infection and a positive nasopharyngeal swab (NPS).

Methods
A retrospective cohort study of inpatient adults empirically treated with antibiotics and subsequent positive NPS during 2018. We compared patients whose antibiotics were stopped within 48 hours of a positive NPS with those whose antibiotics continued.

Results
Empiric antibiotics were continued despite confirmation of a viral respiratory infection in 54 (54%) patients. Consolidation on a chest X-ray (odds ratio [OR], 3.6; 95% confidence intervals [CI], 1.5–8.3; P = 0.003) and a respiratory rate of ≥ 22 breaths per minute at the time of diagnosis (OR, 2.4; 95% CI, 1.1–5.4; P =0.03) were associated with continuation of antibiotics.

Conclusion
An increased respiratory rate upon diagnosis and consolidation on chest X-ray were associated with the physicians' decisions to continue empiric antibiotics after diagnosis of a viral infection.

Résumé

Objectifs
Déterminer les caractéristiques des patients associées à la décision des médecins de poursuivre le traitement empirique par antibiotiques chez les patients atteints d'une infection des voies respiratoires inférieures et ayant un résultat positif par écouvillonnage nasopharyngé (ENP).

Méthodologie
Une étude de cohorte rétrospective menée chez des adultes hospitalisés recevant un traitement empirique par antibiotiques et ayant obtenu un résultat positif par ENP a été

réalisée au cours de l'année 2018. Nous avons comparé les patients qui ont cessé la prise d'antibiotiques dans les 48 heures suivant un résultat positif par ENP et ceux qui ont poursuivi le traitement par antibiotiques.

Résultats

Le traitement empirique par antibiotiques s'est poursuivi chez 54 patients (54 %) malgré la confirmation d'une infection respiratoire virale. La présence d'une consolidation sur la radiographie pulmonaire (rapport de cotes [RC] de 3,6; intervalle de confiance [IC] à 95 % de 1,5 à 8,3; P = 0,003) et la fréquence respiratoire égale ou supérieure à 22 respirations par minute au moment du diagnostic (RC de 2,4; IC à 95 % de 1,1 à 5,4; P = 0,03) sont associées à la poursuite du traitement par antibiotiques.

Conclusion

Une fréquence respiratoire accélérée au moment du diagnostic et la présence d'une consolidation sur la radiographie pulmonaire sont associées aux décisions des médecins de poursuivre le traitement empirique par antibiotiques après le diagnostic d'une infection virale.

Introduction

Studies have shown that up to 50% of antimicrobial prescribing is inappropriate.[1] Inappropriate antibiotic prescribing for lower respiratory tract infections (LRTIs) is the primary driver with reported rates of improper use as high as 65%.[2]

Although most LRTI is because of viruses,[3] it is challenging to reliably identify relevant pathogens in patients with LRTI, leading to a high prevalence of inappropriate antibiotic prescription.[4] A recent study has shown that in patients with radiographic evidence of pneumonia, a pathogen was detected in only 38% of cases, of which 23% were viruses, 11% were bacteria, and 3% were bacterial-viral coinfections.[3] However, rates of bacterial coinfections vary widely in studies from 2%–65%[5] and there is no reliable test to rule out coinfections in patients who have a confirmed viral LRTI. Furthermore, bacterial coinfections were found to be implicate up to 55% of deaths in the swine flu pandemic of 2009.[6] Therefore bacterial coinfections may be of great concern to clinicians, even if a nasopharyngeal swab (NPS) detects a virus. In patients with severe influenza, patient factors such as younger age and lower comorbidities are predictive of acquiring a bacterial coinfection.[7] It may be possible that some of these patient factors also impact the decision of clinicians to continue, discontinue, or change the patient's antibiotics in light of a positive viral swab.

Antimicrobial stewardship programs (ASP) are now a required organizational practice in Canada and have been shown to improve patient care.[8] ASP programs have been successful in improving appropriate antibiotic prescribing, reducing pathogen resistance, and improving clinical outcomes among inpatients for community-acquired pneumonia (CAP) treatment.[9] The use of clinical pathways as an ASP strategy for the management of CAP has been shown to reduce the length of stay and days of intravenous antibiotic therapy.[10]

Hence, we aimed to determine patient characteristics that trigger the continuation of empiric antibiotics in patients with laboratory-confirmed viral respiratory tract infection for the final goal of developing a clinical pathway to improve antibiotic prescribing for the treatment of LRTIs. Additionally, we assessed whether antibiotic management is associated with length of stay, mortality rates, and risk for *Clostridioides difficile* infection.

Methods

This retrospective cohort study was conducted at two tertiary care teaching sites in Hamilton, Ontario, Canada, with 607 and 353 beds, respectively. The study was approved by the Hamilton Integrated Research Ethics Board.

We received a list of all patients admitted during the period between January 1 and December 31, 2018, who had an NPS positive for a respiratory virus from the microbiology lab. Patients were then randomly assigned into rank order and checked for eligibility from the first-ranked patient until the 100 eligible patients were identified. The eligibility criteria were 18 years of age or older, admitted to the medicine service with a formal diagnosis of a lower respiratory tract infection, and started on empiric antibiotics while the results of the NPS were pending. Patients were excluded if they had a history of HIV, febrile neutropenia, or received antibiotics for another indication/infection. We compared the characteristics and presentation of patients in whom antibiotics had been continued with those in whom antibiotics were stopped within 48 hours of the positive NPS results. Our in-house multiplex polymerase chain reaction (PCR) viral panel identifies the following viral pathogens: adenovirus, influenza A, influenza B, metapneumovirus, parainfluenza 1-3, rhino/enterovirus, and respiratory syncytial virus (RSV). This study included patients from 2018 and therefore excluded COVID-19 infections.

Potential predictors for the continuation of empiric antibiotics investigated were age, sex, the presence of respiratory and cardiac comorbidities, consolidation on chest X-ray, fever (≥ 38°C), positive bacterial blood or respiratory culture, white blood cell (WBC) count, type of virus isolated, and the components of the quick sepsis-related organ failure assessment (qSOFA) tool on presentation: high respiratory rate (RR, ≥ 22 breaths/minute [bpm]), an altered level of consciousness (Glasgow coma scale< 15), and decreased systolic blood pressure (SBP; ≤ 100 mmHg). The qSOFA is used to identify patients with a suspected infection that are at risk for a poor outcome. A score of ≥2 is associated with increased mortality and the need for intensive care (ICU) admission.[11] We hypothesized that higher qSOFA scores would be associated with a higher rate of antibiotic continuation post-NPS result. The rate of bacterial co-infection was also determined and defined as a sputum or blood culture that was positive for bacteria deemed to be causal of a respiratory tract infection. The following patient outcomes were evaluated: length of stay, inpatient mortality, and *C. difficile* infection (CDI).

We first conducted a Chi-squared univariate analysis comparing patients who had their antibiotics continued with those who did not and reported odds ratio (OR) and the 95% confidence interval (CI) for the binary data. For nonnormally distributed continuous data, we used the Mann-Whitney U-test. Potential predictors for the continuation of empiric antibiotics with a P-value of < 0.2 in univariate analysis were included in the logistic regression multivariate analysis.

Results

Among 1068 patients with positive NPS, 293 patients were screened for eligibility to achieve the sample size of 100 eligible patients. The most common reason for exclusion was being admitted to another service (37%; Figure 1).

Of the included patients, 52% were male, the median age was 80 (intraquartile range (IQR), 67–88) years, and the median length of stay was 4 (IQR, 2-9) days. The most frequently isolated viruses were Rhino/Enterovirus (36%) and Influenza A/B (37%). Ceftriaxone and azithromycin were the most frequent (37%) antibiotic regimen, followed by levofloxacin (31%). Fifty-four (54%) had their empiric antibiotics continued beyond 48 hours after the positive NPS results. Only 12 patients with a severe illness (qSOFA=2 or 3) were eligible, of which 67% (eight) had their antibiotics continued. Eight patients (8%) had a confirmed bacterial co-infection, of which seven had their antibiotics continued.

Both consolidation on a chest X-ray and a respiratory rate of ≥22 bpm were associated with continuing antibiotics in the

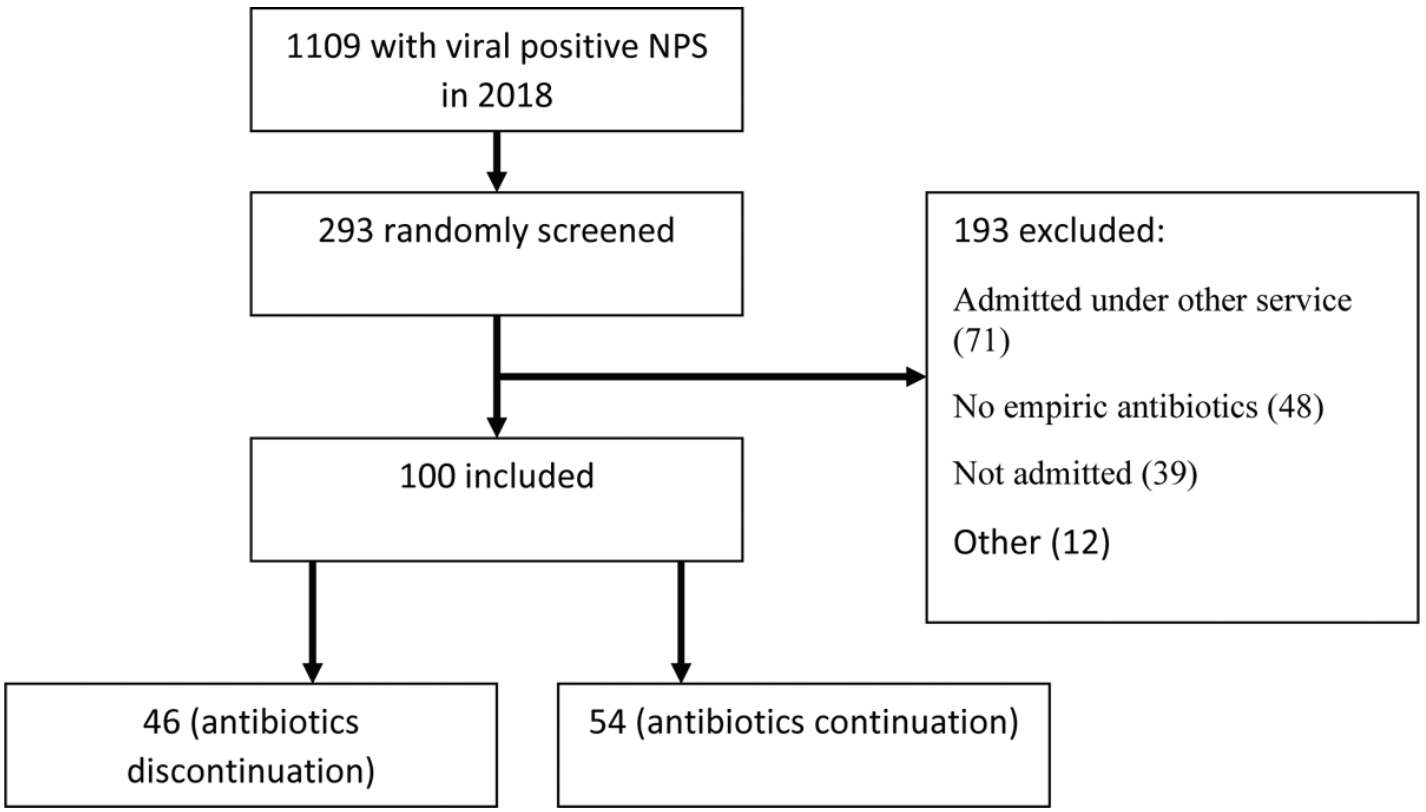

Figure 1. Patient screening.

univariate analysis, whereas male sex, age, WBC count, presence of respiratory or cardiac comorbidities, severity of illness, the isolated virus (P = 0.94; Figure 2), and choice of empiric antibiotic regimen (P = 0.23; Figure 3) were not (Table 1).

In multivariate analysis, consolidation on a chest X-ray (OR, 3.9; 95% CI, 2.4–6.2; P = 0.004) and a respiratory rate of 22 bpm (OR, 2.8; 95% CI, 1.8–4.5; P = 0.02) remained significantly associated with continuing antibiotics whereas WBC count (OR, 1.07; 95% CI, 1.03– 1.12; P = 0.10) and age (OR, –0.01; 95% CI, 0.97–1.00; P = 0.36) were not.

Inpatient mortality or length of stay were not statistically associated with a physician's decision to continue antibiotics (Table 1). Only two cases of *C. difficile infection* occurred (one patient/group).

Discussion

A positive chest X-ray and a high respiratory rate were associated with a physician's decision to continue empiric antibiotics after laboratory confirmation of a viral respiratory tract infection. The type of virus, initial antibiotic choice, comorbidities, and severity of illness were not associated with the decision of continued antibiotics.

We hypothesized that patients with more severe presentations (i.e., a higher qSOFA score) would be more likely to have their antibiotics continued. However, no association between the qSOFA score and the decision to continue antibiotics, and only a higher respiratory rate –one of the qSOFA components- was found to be significantly associated with the decision to continue empiric antibiotics. We may have missed an association because of the small number of severely sick patients. Most patients with qSOFA scores of two and higher were most likely admitted to the ICU and not under a medicine service and were hence, not eligible.

Only 8% of patients had bacterial culture suggesting coinfection, and current literature reports a wide range of bacterial coinfections from 2–65%. However, given limitations in sputum cultures, and difficulties in diagnosing a bacterial coinfection, this likely under-represents the original value. More than half of the patients with a confirmed viral infection had their empiric antibiotic treatment continued; only a few of these had a confirmed bacterial coinfection, because of the lack of a local clinical pathway for the management of these patients. Such pathways may reduce unnecessary continuation of antibiotics[8] in some of these patients, similar to previous studies that have found improvement inappropriate antibiotic ordering for CAP.[9]

Our study is limited by the fact that it is a retrospective study. Hence, we can only hypothesize that antibiotic discontinuation was triggered by a positive NPS but are unable to establish a causal relationship. Additionally, our study was not powered to detect differences in clinical outcomes. Therefore, no conclusions regarding the impact of to continue antibiotics on patient outcomes. Future studies should assess the role of prescriber characteristics and evaluate the effect of continuing versus discontinuing antibiotics on patient-important outcomes

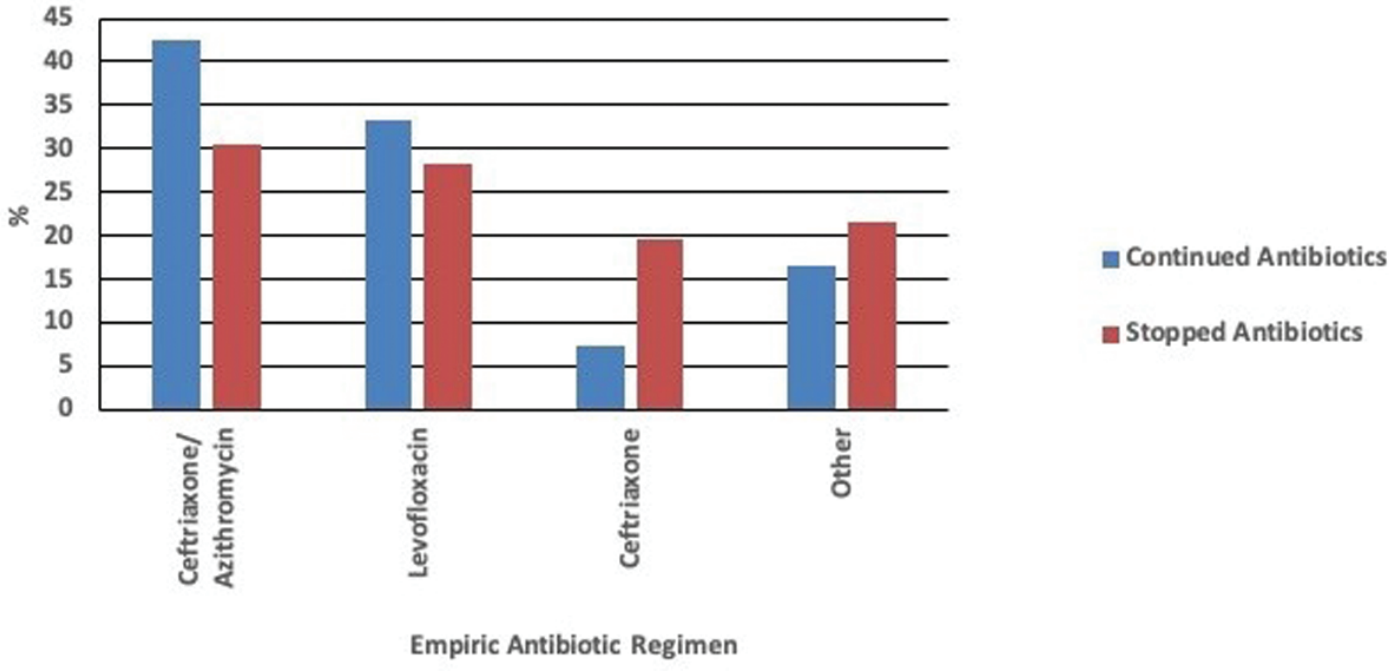

Figure 2. Empiric antibiotic regimen.

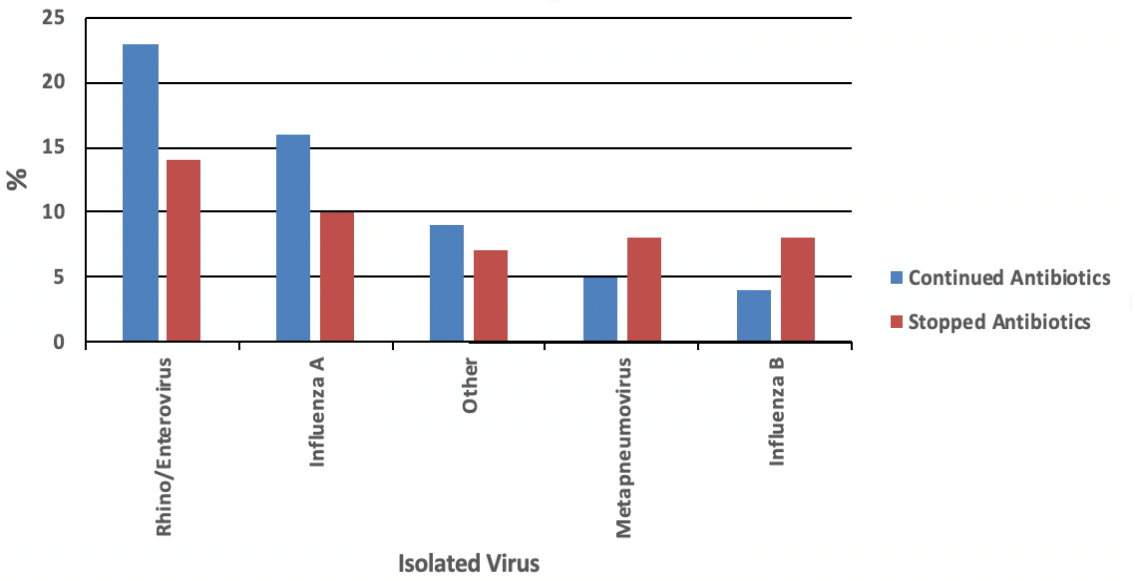

Figure 3. Isolated virus.

Table 1. Clinical Factors.

	Antibiotics continued (n = 54)	Antibiotics stopped (n = 46)	OR/MD (95% CI)	P value
Patient characteristic				
Male	29 (54%)	23 (50%)	1.16 (0.53–2.55)	0.71
Respiratory comorbidity	26 (55%)	21 (45%)	1.11 (0.50–2.43)	0.80
Cardiac comorbidity	46 (53%)	40 (47%)	0.86 (0.28–2.70)	0.8
SBP ≤ 100 mmHg	4 (7%)	4 (9%)	0.84 (0.20–3.56)	0.81
RR ≥ 22 bpm	34 (63%)	19 (41%)	2.42 (1.08–5.41)	0.03[a]
GCS < 15	7 (13%)	7 (15%)	0.83 (0.27–2.57)	0.75
qSOFA = 0	16 (30%)	20 (43%)	–	
qSOFA = 1	30 (56%)	22 (48%)	0.59 (0.25–1.40)	0.23
qSOFA = 2	8 (15%)	4 (9%)	0.41 (0.09–1.60)	0.21
qSOFA = 3	0	0	–	–
Consolidation on CXR	32 (59%)	13 (28%)	3.58 (1.54–8.32)	0.003[a]
Febrile (T ≥ 38 °C)	16 (30%)	13 (28%)	1.07 (0.45–2.55)	0.88
Positive bacterial culture (sputum and blood)	7 (13%)	1(2%)	6.60 (0.80–308.60)	0.099
WBC	9.6 (7.3–14.50)	8.45 (6.125–12)	3.39 (0.26–6.51)	0.09[b]
Age	75 (65.25 to 86.5)	83 (70.5–88.75)	–4.04 (–9.92 to 1.84)	0.07[b]
Outcomes				
Inpatient mortality	3 (6%)	6 (13%)	0.39 (0.09–1.67)	0.19
Length of stay (days)	5 (2.0–9.75)	3 (1.0–8.75)	8.07 (–5.26 to 21.40)	0.195

OR, odds ratio; MD, mean difference; SBP, systolic blood pressure; RR, respiratory rate; bpm, breaths per minute; GCS, Glasgow coma scale; CXR, chest X-ray; WBC, white blood cell count; qSOFA, quick Septic-related Organ Failure Assessment; T, temperature.

[a] statistically significant, [b] Other variables that qualified for multivariate analysis (P value = 0.05–0.2)

such as time to clinical improvement, length of stay, in-patient mortality, and *C. difficile* infection rates.

In conclusion, our study has enhanced the understanding of physician decision-making regarding antibiotics in patients with laboratory-confirmed viral respiratory tract infections. An increased respiratory rate and consolidation on chest X-rays were associated with the physician decision to continue antibiotics after laboratory confirmation of a viral infection.

Disclosure

Approval for the study was granted by The Hamilton Integrated Research Ethics Board (HiREB) which represents the institutions of Hamilton Health Sciences, St. Joseph's Healthcare Hamilton, Research St. Joseph's-Hamilton and the Faculty of Health Sciences at McMaster University.

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