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ORIGINAL RESEARCH

An antibiotic stewardship exercise in the ICU: building a treatment algorithm for the management of ventilator-associated pneumonia based on local epidemiology and the 2016 Infectious Diseases Society of America/American Thoracic Society guidelines

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Introduction: Management of ventilator-associated pneumonia (VAP), the most common infection in patients on mechanical ventilation, should be tailored to local microbiological data. The aim of this study was to determine susceptibility patterns of organisms causing VAP to develop a treatment algorithm based on these findings and evidence from the literature.

Materials and methods: This is a retrospective analysis of the microbiological etiology of VAP in the intensive care unit (ICU) of a Lebanese tertiary care hospital from July 2015 to July 2016. We reviewed the latest clinical practice guidelines on VAP and tried to adapt these recommendations to our setting.

Results: In all, 43 patients with 61 VAP episodes were identified, and 75 bacterial isolates caused VAP. Extensively drug-resistant (XDR) *Acinetobacter baumannii* was the most common organism (37%), and it had occurred endemically throughout the year. *Pseudomonas aeruginosa* was the next most common organism (31%), and 13% were XDR. Enterobacteriaceae (15%) and *Stenotrophomonas maltophilia* (12%) shared similar incidences. Our algorithm was based on guidelines, in addition to trials, systematic reviews, and meta-analyses that studied the effectiveness of available antibiotics in treating VAP.

Conclusion: Knowing that resistance can rapidly develop within a practice environment, more research is needed to identify the best strategy for the management of VAP.

Keywords: ventilator-associated pneumonia, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, local epidemiology, carbapenem-sparing strategy, guidelines

Introduction

Ventilator-associated pneumonia (VAP) is the most well-known nosocomial infection complicating the course of intubated patients and the leading cause of death in critical care settings worldwide, in addition to being the first cause of antibiotic prescription in intensive care units (ICUs) despite the development of prevention bundles.[1] Episodes caused by multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) organisms further aggravate the situation, thus imposing a considerable clinical and economic burden, along with the limited and exhausted antibiotic armamentarium.[2]

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Infection control and antimicrobial stewardship programs are mainstay strategies for curbing down resistance.[3] Specifically, antibiotic treatment guidelines constitute a core element of antimicrobial stewardship programs.[3] Yet, clinical practice guidelines developed by international societies need to be tailored according to local epidemiology. Timely surveillance for local microbiological data is extremely important in predicting the type of resistance that may be present in the etiologic agent causing a clinical infection.[3]

In July 2016, the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) updated their clinical practice guidelines for the management of hospital-acquired pneumonia (HAP) and VAP.[4]

In this study, our aim was to determine susceptibility patterns of the leading organisms causing VAP in the ICU of our facility in order to develop a treatment algorithm based on the 2016 IDSA/ATS guideline recommendations. We also aimed to review available therapeutic options for the treatment of resistant organisms causing VAP, based on evidence from the literature.

Materials and methods

Setting and study design

This is a retrospective analysis of the microbiological etiology of VAP in the ICU in a tertiary care hospital in Lebanon. Data were retrieved from the medical microbiology laboratory logbooks and patients' electronic medical records from July 2015 to July 2016. Data included bacterial species isolated from endotracheal aspirate specimens along with their antibiotic susceptibility patterns. Duplicate isolates, colonizers, and organisms causing respiratory tract infections other than VAP were omitted from the analysis.

The distribution of pathogens causing VAP was plotted against time. Endemic pathogens in the ICU were identified, as well as other organisms that caused occasional epidemics. Antibiotic history within 90 days of the VAP episodes was also reviewed. As recommended by the World Health Organization (WHO), antimicrobial consumption was reported in defined daily dose (DDD) per 100 bed day (BD), a standardized figure that provides a degree of comparison among inpatients in different hospitals.[5]

Microbiological studies and breakpoints of resistance

Bacterial identification was performed according to standard microbiologic procedures. Antibiotic susceptibility testing was performed using the Kirby–Bauer disk diffusion test on Mueller–Hinton agar (Oxoid Ltd.) according to standard procedures. Culture plates were incubated at 37°C for 24 hours. The Clinical and Laboratory Standards Institute (CLSI) breakpoints for the available systemic antibiotics were used to determine susceptibility at our facility.[6] No interpretation data are available for tigecycline susceptibility against *Acinetobacter baumannii* from CLSI[6] or the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[7] regardless of the testing method. Therefore, we applied clinical breakpoints suggested by Jones et al[8] (susceptible [S] ≥ 16 mm, intermediate [I] 13–15 mm, and resistant [R] ≤12 mm). Neither CLSI[6] nor EUCAST[7] guideline provides disk diffusion zone diameter breakpoints for colistin (CST) susceptibility against *A. baumannii*. In our center, CST susceptibility was determined using the disk diffusion method with the following breakpoints: S ≥ 11 mm and R ≤ 8 mm.[9]

Gram-negative organisms were labeled as MDR or XDR as described by Magiorakos et al.[10] XDR *A. baumannii* in our institution was carbapenem resistant and susceptible only to polymyxins ± glycylcyclines. *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* were labeled XDR when resistant to all tested available antibiotics except for the polymyxins. Ceftolozane/tazobactam was not available for use in Lebanon at the time of the study.

In our study, a pathogen is considered endemic when challenges from admitting patients colonized or infected with this organism are constantly present.[11] Yet, an organism is considered as epidemic where there is an unexpected increase in cases of infections due to this pathogen for a short period of time.[11]

Development of our own recommendations and VAP treatment algorithm

The latest clinical practice guidelines endorsed by IDSA/ATS on the management of adults with HAP/VAP were reviewed.[4] We tried to adapt the stated recommendations to our ICU epidemiology, when applicable. For certain resistant organisms, no specific recommendations were made; hence, we conducted a profound literature search in order to base our proposed choices on solid evidence. Our propositions were based on trials, case reports, systematic reviews, and meta-analyses that studied the effectiveness of specific antibiotic combinations in the treatment of VAP caused by MDR and XDR organisms. Finally, we proposed an algorithm for empiric data and targeted antibiotic therapy for VAP as a basis for antibiotic stewardship in the ICU of our facility.

Ethical approval

The institutional review board committee of Makassed General Hospital approved this study.

Informed consent

No informed consent was required due to the retrospective nature of this study. During the data collection phase, a special form was used where patient initials and case numbers were only included. At a later stage, a different number was assigned to each of our cases to safeguard patient privacy. All contributing authors performed data entry and analysis as well as the drafting of the paper.

Results

From July 2015 to July 2016, 776 patients were admitted to the ICU of our facility where total patient days were 4792 and total ventilator days were 1533. During this period, 43 patients with 61 VAP episodes were identified, of which 47 (77%) were monomicrobial episodes and 14 (23%) were polymicrobial episodes. From all organisms isolated from endotracheal aspirate specimens (N=108 isolates), 75 isolates were implicated in causing VAP during this period: 72 gram-negative isolates (96%) and three gram-positive isolates (4%; Table 1).

Among the gram-negative isolates, *A. baumannii* predominated (37.33%), followed by *P. aeruginosa* (30.76%), Enterobacteriaceae (14.67%), and *S. maltophilia* (12%). Antibiotic susceptibility patterns are provided in Table 1. Among *A. baumannii* (28 isolates), 92.86% were XDR, 3.57% were MDR, and 3.57% were PDR. With respect to *P. aeruginosa* (23 isolates) susceptibility to antibiotics, 56.5% were susceptible to carbapenems, 69.6% to piperacillin/tazobactam (TZP), 73.9% to ceftazidime (CAZ), and 78.3% to levofloxacin (LVX) and 13% were XDR. For Enterobacteriaceae (11 isolates), 81.8% were susceptible to cefepime (FEP), 72.7% to third-generation cephalosporins (3GC) and TZP, and 81.8% to fluoroquinolones (FQ). All isolates were fully susceptible to carbapenems. Among *S. maltophilia* (nine isolates), 55.6% were susceptible to CAZ, 77.8% to LVX, and 88.9% to trimethoprim/sulfamethoxazole (TMP/SMX). One *S. maltophilia* isolate was resistant to CAZ, LVX, and TMP/SMX, yet found susceptible to CST and thus was considered XDR. *S. aureus* was the only gram-positive species isolated for which one of the three isolates identified was methicillin resistant.

The temporal distribution of ICU pathogens causing VAP is shown in Table 2. XDR *A. baumannii* was isolated from ICU patients almost every month throughout the study period.

According to the hospital infection control data, there was a constant challenge from admitting patients colonized or infected with this organism to ICU. Subsequently, *A. baumanii* was considered as an endemic organism. XDR *P. aeruginosa* was recovered sporadically from three cases on three separate occasions during the year, and each was separated by a 2- to 4-month interval. It was considered as an organism causing separate ICU epidemics. However, non-XDR *P. aeruginosa* is a common organism, isolated in a continuous manner throughout the year. It has been equally susceptible to LVX, CAZ, FEP, and TZP. Only one isolate showed resistance to FEP plus LVX, and another was resistant to TZP plus LVX. With regard to Enterobacteriaceae, 3GC-sensitive isolates predominated over 3GC-resistant ones and were regularly isolated throughout the year. 3GC-resistant species were isolated sporadically in 2 months only and separated by a 6-month interval. The most active antibiotics against the recovered Enterobacteriaceae were LVX and FEP. None of the isolates were resistant to FEP plus LVX or TZP plus LVX. Both XDR *S. maltophilia* and methicillin-resistant *S. aureus* (MRSA) were isolated in 1 month only.

In our ICU, antimicrobial consumption measured using DDD/100 BD showed that carbapenems were the most commonly used broad-spectrum antimicrobials (16.7 DDD/100 BD), followed by FQ (9.68 DDD/100 BD) and CST (5.74 DDD/100 BD; Figure 1).

Discussion

In this study, we described the microbiological etiology of VAP in patients admitted to an ICU from July 2015 to July 2016, and we proposed an antibiotic treatment pathway based on the most recent international guidelines.

Current local epidemiology of VAP

The microbiological ecology and the frequency of specific pathogens causing VAP vary by hospital, patient population, exposure to antibiotics, and type of ICU patients, and they change over time, emphasizing the need for timely local surveillance data.[2] According to the 2016 IDSA/ATS guidelines on VAP,[4] each hospital should generate its own antibiograms to guide health care professionals in the optimal choice of antimicrobials to curb down resistance caused by the exposure to unnecessary antibiotics.

Studies from the Middle East involving the incidence, microbiology, and antimicrobial susceptibility patterns of bacteria causing VAP are scarce. Only one study from Lebanon was published by Kanafani et al[12] in 2003. It was a prospective observational cohort study at a tertiary-care center

Table 1 Distribution of bacteria causing VAP according to their antibiotic susceptibility patterns

Organisms	Number of isolates	Percentage from own species (%)	Percentage from total (%) (n=75 isolates)
Gram-negative species	72		96
A. baumanii	28		37.33
MDR	1	3.57	1.33
XDR	26	92.86	34.67
PDR	1	3.57	1.33
P. aeruginosa	23		30.67
TZP S	16	69.57	21.33
TZP R	7	30.43	9.33
CAZ S	17	73.91	22.67
CAZ R	6	26.09	8
FEP S	16	69.57	21.33
FEP R	7	30.43	9.33
AMK S	15	65.22	20
AMK R	8	34.78	10.67
LVX S	18	78.26	24
LVX R	5	21.74	6.67
CAR S	13	56.52	17.33
CAR R	10	43.48	13.33
FEP and LVX R	4	17.39	5.33
TZP and LVX R	4	17.39	5.33
(FEP and LVX R) but CAR S	0	0	0
(TZP and LVX R) but CAR S	1	4.34	1.33
Non-XDR	20	86.96	26.67
XDR	3	13.04	4
Enterobacteriaceae	11		14.67
3GC S	8	72.73	10.67
3GC R	3	27.27	4
TZP S	8	72.73	10.67
TZP R	3	27.27	4
FEP S	9	81.82	12
FEP R	2	18.18	2.67
FQ S	9	81.82	12
FQ R	2	18.18	2.67
CAR S	11	100	14.67
CAR R	0	0	0
FEP and LVX R	1	9.09	1.33
TZP and LVX R	1	9.09	1.33
S. maltophilia	9		12
LVX S	7	77.78	9.33
LVX R	2	22.22	2.67
CAZ S	5	55.56	6.67
CAZ R	4	44.44	5.33
TMP/SMX S	8	88.89	10.67
TMP/SMX R	1	11.11	1.33
CST S[a]	NA	NA	NA
XDR[a]	1	11.11	1.33
B. cepacia	1		1.33
Gram-positive species	3		4
S. aureus	3		4
MET S	2	66.67	2.67
MET R	1	33.33	1.33

Notes: [a]*S. maltophilia* is not tested routinely in the hospital for CST susceptibility, unless it is resistant to other alternatives (being an XDR). One isolate was XDR and was found susceptible to CST.

Abbreviations: *A. baumannii*, *Acinetobacter baumannii*; AMK, amikacin; *B. cepacia*, *Burkholderia cepacia*; CAR, carbapenem; CAZ, ceftazidime; CST, colistin; FEP, cefepime; FQ, fluoroquinolones; LVX, levofloxacin; MDR, multi-drug resistant; MET, methicillin; NA, not available; *P. aeruginosa*, *Pseudomonas aeruginosa*; PDR, pandrug resistant; R, resistant; S, susceptible; *S. aureus*, *Staphylococcus aureus*; *S. maltophilia*, *Stenotrophomonas maltophilia*; TMP/SMX, trimethoprim/sulfamethoxazole; TZP, piperacillin/tazobactam; VAP, ventilator-associated pneumonia; XDR, extensively drug resistant; 3GC, third-generation cephalosporins.

Table 2 Temporal distribution of bacteria causing VAP (number of isolates) over 12-month period from July 2015 to July 2016

Organisms	July 2015	August 2015	September 2015	October 2015	November 2015	December 2015	January 2016	February 2016	March 2016	April 2016	May 2016	June 2016	July 2016
A. baumannii	2	1	3	1	2	0	0	4	4	2	2	4	3
XDR	2	1	3	1	1	0	0	4	4	2	1	4	3
P. aeruginosa	1	1	1	1	3	0	0	6	2	0	2	3	3
TZP S	1	1	1	1	2	0	0	4	2	0	2	1	1
FEP S	1	1	1	1	2	0	0	4	1	0	2	2	2
CAZ S	1	1	1	1	2	0	0	3	1	0	2	2	2
LVX S	1	1	1	1	2	0	0	5	1	0	2	3	1
FEP or LVX S	1	1	1	1	1	0	0	5	1	0	2	3	2
TZP or LVX S	1	1	1	1	2	0	0	5	2	0	2	3	1
FEP and LVX R	0	0	0	0	0	0	0	0	1	0	0	0	0
TZP and LVX R	0	0	0	0	0	0	0	0	0	0	0	0	1
Non-XDR	1	1	1	1	2	0	0	5	2	0	2	3	2
XDR	0	0	0	0	1	0	0	1	0	0	0	0	1
Enterobacteriaceae	1	0	2	1	0	1	0	0	2	0	1	1	2
LVX S	0	0	1	1	0	1	0	0	2	0	1	1	2
TZP S	1	0	1	1	0	1	0	0	1	0	1	1	1
FEP S	1	0	0	1	0	1	0	0	2	0	1	1	2
3GC S	1	0	0	1	0	1	0	0	1	0	1	1	2
FEP or LVX S	1	0	1	1	0	1	0	0	2	0	1	1	2
TZP or LVX S	1	0	1	1	0	1	0	0	2	0	1	1	2
3GC R	0	0	2	0	0	0	0	0	1	0	0	0	0
FEP and LVX R	0	0	1	0	0	0	0	0	0	0	0	0	0
TZP and LVX R	0	0	1	0	0	0	0	0	0	0	0	0	0
S. maltophilia	0	0	0	0	0	0	1	3	1	0	0	0	4
LVX S	0	0	0	0	0	0	1	3	1	0	0	0	2
CAZ S	0	0	0	0	0	0	1	1	0	0	0	0	3
XDR	0	0	0	0	0	0	0	0	0	0	0	0	1
MRSA	0	0	0	0	0	0	0	1	0	0	0	0	0

Abbreviations: *A. baumannii*, *Acinetobacter baumannii*; CAZ, ceftazidime; FEP, cefepime, LVX, levofloxacin; MRSA, methicillin-resistant *S. aureus*; *P. aeruginosa*, *Pseudomonas aeruginosa*; R, resistant; S, susceptible; *S. aureus*, *Staphylococcus aureus*; *S. maltophilia*, *Stenotrophomonas maltophilia*; TZP, piperacillin/tazobactam; VAP, ventilator-associated pneumonia; XDR, extensively drug resistant; 3GC: third-generation cephalosporins.

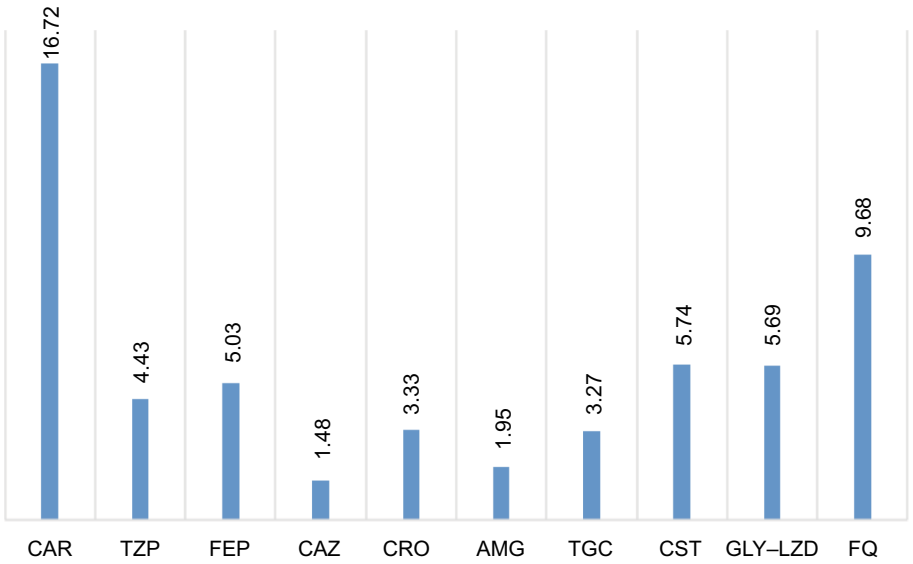

Figure 1 Antibiotic consumption in the ICU of our facility during the study period (July 2015–July 2016) reported in DDD/100 BD.
Note: x-axis, type of antimicrobial; y-axis, DDD/1000 bed days.
Abbreviations: AMG, aminoglycosides; BD, bed day; CAR, carbapenems; CAZ, ceftazidime; CRO, ceftriaxone; CST, colistin; DDD, defined daily dose; FEP, cefepime; FQ, fluoroquinolones; GLY, glycopeptides (vancomycin and teicoplanin); ICU, intensive care unit; LZD, linezolid; TGC, tigecycline; TZP, piperacillin/tazobactam.

involving all patients admitted to the ICU and respiratory care unit from March to September 2001 who were on mechanical ventilation for at least 48 hours. The most commonly isolated organisms were gram-negative bacilli, among which *Acinetobacter* and *Pseudomonas* species were predominant. With respect to the antibiotic susceptibility pattern, 50% of the gram-negative isolates were antibiotic resistant, yet 91% were still carbapenem susceptible at that time.[12] Our study is the second from the country involving VAP etiology in the era of resistance and limited treatment options.

In our facility, gram-negative bacteria predominated, representing 96% of the total respiratory isolates. Compared to findings by Kanafani et al[12] in 2003, *A. baumannii* and *P. aeruginosa* are still the leading organisms; however, the emergence of carbapenem-resistant strains in both species is striking in our 2016 series. According to recently published antimicrobial resistance data from hospitals all across Lebanon, *A. baumannii* and *P. aeruginosa* have emerged as frequent nosocomial pathogens, and carbapenem susceptibility has reached 18% and 73%, respectively, in this nationwide study.[13] This rate of antimicrobial resistance constitutes a major threat in critical care units.

Temporal distribution of pathogens causing VAP

With respect to the temporal distribution of pathogens causing VAP throughout the study period (Table 2), XDR *A. baumannii* has shown an endemic pattern in our ICU. Likewise, it has been increasingly associated with nosocomial epidemics in the ICUs of our region[14] and worldwide.[15] Of particular concern is its environmental resilience, resulting in sustained outbreaks and endemic situations, as well as its inherent and acquired mechanisms of resistance to antibiotics, rendering it the prototype of XDR bacteria.[16] Non-XDR *P. aeruginosa* is another endemic pathogen in our facility, yet isolation of XDR strains was sporadic. Acquisition of XDR *P. aeruginosa* in the ICU, causing these epidemic bouts, depends on variables including colonization pressure created by carriers and antibiotic-selective pressure.[17]

Antibiotic consumption in critical care

Critical care units manage only a small proportion of hospitalized patients but administer disproportionately large quantities of broad-spectrum antimicrobials, which are implicated in resistance.[18] In Lebanon, a national surveillance system for antimicrobial resistance and antimicrobial consumption is not yet established. However, resistance data and antibiotic prescription patterns are derived from published multicenter studies.[13,19] Our results showed that carbapenems were the most widely prescribed during the study period (16.72 DDD/100 BD), followed by other broad-spectrum antibiotics, including third- and fourth-generation cephalosporins (total of 9.83 DDD/100 BD) and FQ (9.68 DDD/100 BD; Figure 1). A recently published multicenter cross-sectional study assessed antibiotic consumption from pharmacy electronic records in 27 nonteaching Lebanese

hospitals during 2012.[19] Antibiotic consumption was stratified according to the geographical location, occupancy rate, and number of beds, including the number of ICU beds. Results showed that the average carbapenem consumption in ICUs with nine or more beds reached 6.16 DDD/100 BD, which is much less in comparison with our results. This major difference in carbapenem use may be attributed to the type of facilities described. Ours is a tertiary-care teaching hospital, and the ones reported by Iskandar et al[19] were primary- and secondary-care nonteaching health care facilities. Moreover, carbapenems are the drug of choice in cases of sepsis in the hospital protocols due to the increasing prevalence of extended spectrum beta lactamase (ESBL)-producing organisms in the community and hospital flora, according to recent surveillance data.[13,20] Yet, the extensive use of carbapenems for the management of resistant organisms led to the selection of carbapenem-resistant species.[14,21] Moreover, findings from a recently published Lebanese study showed that recent antibiotic intake was an independent risk factor associated with the fecal carriage of ESBL-producing Enterobacteriaceae in long-term care facility residents.[22]

Strategy for choosing empiric therapy for VAP

The cumbersome task of choosing appropriate empiric antibiotics for VAP remains. In addition, adequate timing of antibiotic administration, ideally within the first hour, is an essential element in determining the outcome of critically ill patients with infection.[23] Combination antibiograms are important tools to optimize empiric therapy in the ICU through identifying which antimicrobial combinations give the highest likelihood of having at least one active agent against all likely causative pathogens in a specific disease state (VAP), thereby minimizing prolonged delays in instituting appropriate antimicrobial therapy.[24] Combination antibiograms are advantageous to traditional ones because they focus on the susceptibility of potential second agents for combination (FQ) in the setting of resistance to the primary agent (the beta-lactam).[24]

According to our results, empiric therapy targeting, first, XDR *A. baumannii* is highly justified, especially because it has been an endemic pathogen in our facility, along with its highest incidence in VAP etiology (Tables 1 and 2). Second, both *P. aeruginosa* and Enterobacteriaceae susceptible to FEP plus LVX or to TZP plus LVX represented ~95% and ~99% of total isolates, respectively (Table 1). This would give us an at least 95% chance of using either combination for targeting susceptible strains of both organisms. Regarding gram-positive bacteria, *S. aureus* represented 4% of all isolated species, among which 67% were still methicillin susceptible (Table 1). Thus, we chose not to include MRSA in the empiric therapy for VAP unless there is evidence of previous MRSA colonization or contact with another colonized/infected subject. Otherwise, the chosen empiric antimicrobial therapy should cover methicillin-susceptible strains. Therefore, empiric therapy should be broadened to include a beta-lactam/beta-lactamase inhibitor (TZP) plus an antipseudomonal fluoroquinolone (LVX), plus an anti-gram-negative antibiotic targeting XDR *Acinetobacter* strain. At a later stage, this regimen will be replaced by definitive therapy once deep tracheal aspirate culture results and corresponding antibiotic susceptibility patterns are available (Figure 2).

Treatment options for specific organisms and streamlining antibiotic therapy in VAP in era of resistance

Once deep tracheal aspirate culture results are available, empiric therapy should be replaced by targeted therapy based on susceptibility patterns and available therapeutic agents.[4] Following are treatment options for each specific organism (Figure 2).

XDR *A. baumannii*

Almost all the *A. baumannii* isolates in our series were resistant to carbapenems, yet were still susceptible to CST and tigecycline. Susceptibility to sulbactam was not tested since it is not available in the country. The 2016 IDSA/ATS guidelines on VAP expert panel recommended against the use of tigecycline owing to its decreased therapeutic efficacy in VAP and increased mortality rate in comparison to CST-containing regimens.[4,25] Thus, intravenous CST is the only remaining therapeutic option for such cases. Yet, it is well known for its nephrotoxic and neurotoxic profiles.[26] The use of adjunctive therapies with additive or synergistic effects to CST was profoundly discussed in the 2016 IDSA/ATS guidelines.[4] The panel recommended the use of adjunctive aerosolized CST, since it improved clinical outcomes without increasing harms.[27] Conversely, adjunctive rifampicin did not improve outcomes[28] and, therefore, was not recommended. Accordingly, we join the guidelines in adding intravenous plus inhaled CST to our selected empiric treatment regimen for VAP. After definitive culture results are obtained indicating the isolation of XDR *A. baumannii*, intravenous plus inhaled CST only will be used, and all other antibiotics will be discontinued. If cultures are negative for *A. baumannii*, CST is discontinued.

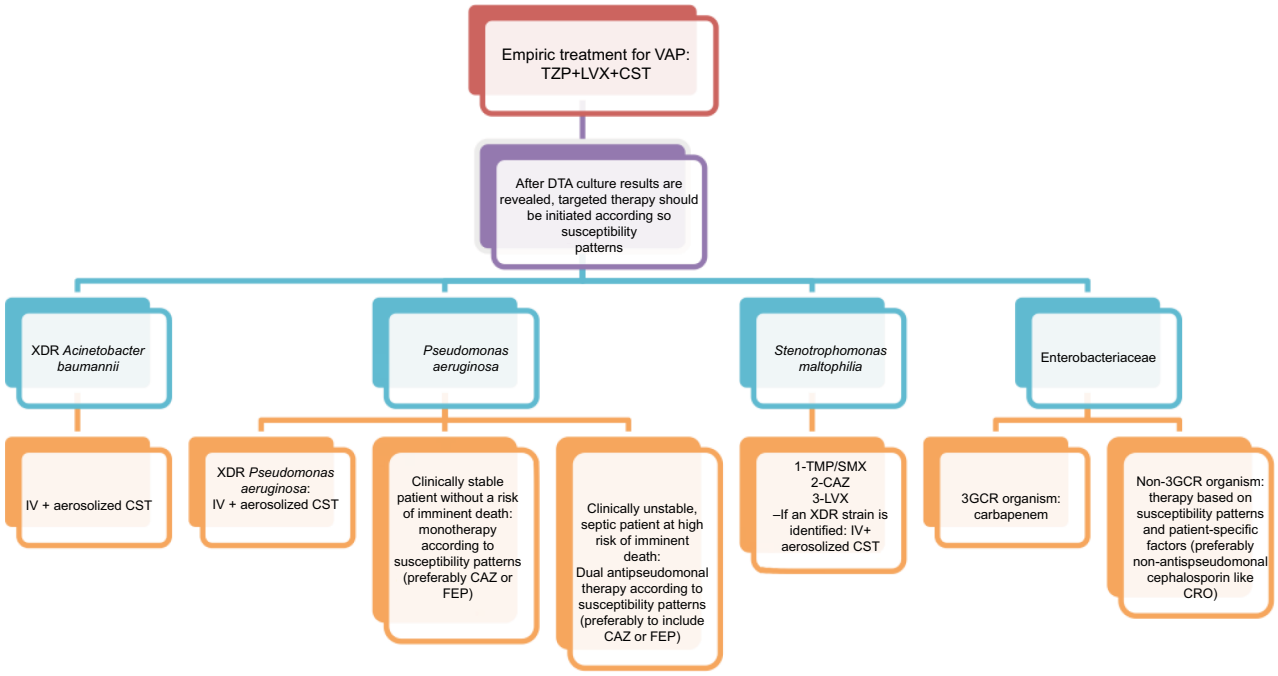

Figure 2 Our proposed treatment algorithm for empiric and targeted treatment of VAP.
Abbreviations: *A. baumannii*, *Acinetobacter baumannii*; CAZ, ceftazidime, CRO, ceftriaxone; CST, colistin; DTA, deep tracheal aspirate; FEP, cefepime; IV, intravenous; LVX, levofloxacin; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. maltophilia*, *Stenotrophomonas maltophilia*; TMP/SMX, trimethoprim/sulfamethoxazole; TZP, piperacillin/tazobactam; VAP, ventilator-associated pneumonia; XDR, extensively drug resistant; 3GCR, third-generation cephalosporin resistant.

P. aeruginosa

For the empiric treatment of suspected VAP due to *P. aeruginosa,* double coverage with two antipseudomonal antibiotics from different classes is warranted in patients with risk factors for resistance.[4] This applies in units where the rate of resistance to any of the antipseudomonal agents is greater than 10%. This 10% threshold for deciding whether to prescribe two antipseudomonal agents was chosen by the expert panel of the IDSA/ATS guidelines with the aim of optimizing empiric therapy.[4] When applicable, individual ICUs may choose to modify this threshold according to their current local microbiologic data and patient-related risk factors.[4] The choice of definitive therapy should be based on antibiotic susceptibility patterns.[4] These guidelines state that combination therapy using two antibiotics is indicated in patients who remain in septic shock or who are at a high risk for death with a documented *Pseudomonas* infection.[4] The expert panel of the IDSA/ATS guidelines did not prefer a specific regimen against documented *Pseudomonas* infection.[4] However, imipenem may have outcomes inferior to other regimens based on a systematic review of randomized trials by Zilberberg et al.[29] However, no recommendation was made against using imipenem, since the results obtained were derived from trials limited by risk of bias and imprecision.[4] As for monotherapy, it is preferably used in clinically stable patients who are not in septic shock and not at a high risk for death.[4] Aminoglycoside monotherapy should not be used due to poor lung tissue penetration, resulting in no detectable antipseudomonal activity within bronchial secretions despite therapeutic aminoglycoside serum in patients with *Pseudomonas* pulmonary infection.[30] Moreover, there is a lack of studies evaluating the effects of aminoglycoside monotherapy in VAP.[4] In settings with a high prevalence for XDR *P. aeruginosa*, routine antimicrobial susceptibility testing should include assessment of its sensitivity to polymyxins.[4] Accordingly, for the empiric management of *P. aeruginosa* in our facility, we propose to use FEP plus LVX or TZP plus LVX for double coverage. With regard to direct therapy, CAZ or FEP monotherapy is preferred when *Pseudomonas* isolates are susceptible to it. In our facility, minimal inhibitory concentration (MIC) determination is not routinely performed; thus, we propose using prolonged infusions of high-dose FEP.[31] When *Pseudomonas* is proved to be XDR, only intravenous plus inhaled CST is to be used.

ESBL-producing Enterobacteriaceae

ICUs in the USA and Europe have witnessed an increase in the incidence of ESBL-producing Enterobacteriaceae infections.[32] The optimum treatment for infections due to ESBL-producing pathogens has been a subject of debate.[33]

Carbapenems have been considered the agents of choice against these serious infections.[34] However, the emerging and rapid spread of carbapenem resistance in different gram-negatives, including Enterobacteriaceae, has led to initiating carbapenem-sparing strategies and alternative therapeutic approaches for the treatment of ESBL infections.[35] Empirical treatment covering ESBL-producing Enterobacteriaceae should be based on the following criteria: geographical areas, epidemiological settings, and individual risk factors.[36] FEP and the β-lactam-β-lactamase inhibitors (BLBLIs) have been the most widely studied carbapenem-sparing options based on their favorable in vitro susceptibility profile to ESBL-producing organisms.[37]

BLBLIs such as TZP have been recommended as an alternative to carbapenems for ESBLs.[38] In clinical practice, BLBLIs are often perceived as inferior to carbapenems in this setting, although there is no strong supporting evidence.[38] The most relevant studies in this topic came to different conclusions. In a single-center retrospective cohort study over 7 years involving 331 patients with bacteremia caused by ESBL-producing Enterobacteriaceae, Tamma et al[39] found that the risk of mortality at day 14 in patients receiving TZP was two times higher than in those who were empirically treated with carbapenems. This finding was not confirmed by another multinational prospective cohort study by Guttiérez-Guttiérez et al[40] who showed that BLBLIs, if active in vitro and used at appropriate doses, appear to be as effective as carbapenems for empiric and targeted ESBL-producing Enterobacteriaceae among relevant subgroups, including organism, source of infection, or severity of illness. Different factors may explain such divergent conclusions, including the geographic variations in the distribution of ESBL phenotypes where the enzyme background plays a significant role and the likely source of infection reflecting the inoculum effect.[37] The results of a randomized controlled study (MERINO trial) comparing TZP to meropenem for the definitive treatment of bacteremia caused by ceftriaxone non-susceptible *Escherichia coli* and *Klebsiella* spp. are definitely awaited to resolve this important issue (MERINO, ClinicalTrials.gov: NCT02176122).[41]

FEP possesses an in vitro activity against ESBL-producing Enterobacteriaceae. Like TZP, the difference between in vitro activity and outcomes in infected patients may be due to the presence of a significant inoculum effect for ESBL producers against FEP.[42] One retrospective study showed a trend toward increased mortality in patients with ESBL-producing Enterobacteriaceae bacteremia treated empirically with FEP as compared to carbapenems, yet this trend did not reach statistical significance.[43] However, other patient-specific characteristics, most notably severity of illness, were more significant predictors of patient outcomes.[43] In another multicenter retrospective study between 2002 and 2007, Lee et al[44] showed that FEP is a potentially effective option for treating bacteremia caused by ESBL-producing Enterobacteriaceae, but only if the MIC of the infecting organism was sufficiently low (i.e., ≤1 μg/mL). A more recent study by Wang et al[45] compared the empiric use of FEP to carbapenems in propensity score-matched cohort patients with ESBL-producing organisms. Similar to the findings by Chopra et al,[43] a nonsignificant trend toward increased mortality was observed in patients treated with FEP versus those treated with carbapenems.

In our series, 3GC-resistant Enterobacteriaceae represented 4% of the total isolates causing VAP. In addition, Enterobacteriaceae isolates resistant to FEP plus LVX or to TZP plus LVX represented 1.33% of the total isolates (Table 1). Accordingly, we elect to avoid carbapenem use in the empiric management of VAP despite the possibility of being caused by ESBL organisms and stick to the previously stated combination regimen (FEP plus LVX plus CST) awaiting culture results. The 2016 IDSA/ATS guidelines on VAP expert panel did not identify a preferable agent for the definitive treatment of VAP due to ESBL-producing Enterobacteriaceae, due to its low confidence in the available literature.[4] If cultures show the presence of 3GC-resistant Enterobacteriaceae, all empiric antibiotics are discontinued and a carbapenem is initiated. If a non-3GC-resistant organism is isolated, therapy should be based on the results of antimicrobial susceptibility testing and patient-specific factors. The chosen antibiotic should be of the narrowest spectrum possible.

S. maltophilia

S. maltophilia is among the most commonly isolated organisms from patients hospitalized with pneumonia in the US and Europe.[32] Risk factors for ICU-acquired *S. maltophilia* colonization and/or infection are prolonged use of broad-spectrum antibiotics, prolonged duration of mechanical ventilation, severity of underlying disease, chronic lung disease, and tracheostomy.[46] This organism is well known for its intrinsic and acquired multidrug resistance to beta-lactam antibiotics, aminoglycosides, macrolides, and tetracyclines.[46] In the 2016 IDSA/ATS guidelines on VAP, no specific recommendations were made for this organism, yet empiric therapy against gram-negative bacilli other than *P. aeruginosa* is warranted, according to local microbiological data.[4] TMP/SMX is the recommended first-line treatment option, not to mention that CST has also shown promising in vitro activity among

other suggested alternatives.[47] In our series, *S. maltophilia* represented 12% of the total isolates, of which 56% were CAZ susceptible and 78% were LVX susceptible (Table 1). Therefore, the inclusion of LVX in our selected empiric regimen would cover the susceptible strains and CST would cover the rest, pending culture results. Definitive therapy is based on results of antibiotic susceptibility. TMP/SMX is the preferred agent in cases of susceptible strains, followed by CAZ and LVX in cases of susceptibility, as well. Intravenous and inhaled CST is the last resort treatment option if XDR *S. maltophilia* is isolated.

Limitations and strengths

The major limitation of this study is that our results and the proposed algorithm cannot be generalized to other units. Our suggestions may not be even applied in the same unit at all times due to the dynamic bacterial ecology of each ICU that varies with time due to several factors, namely, antimicrobials consumption.[2] Yet, this limitation shows the importance of the continuous surveillance of antimicrobial resistance in each ICU.[4] It similarly highlights the fact that the treatment of nosocomial infections should be tailored according to local antimicrobial susceptibility patterns. In addition, this study demonstrates an exercise in antimicrobial stewardship and illustrates the road map for creating local treatment guidelines of nosocomial infections.

Conclusion

VAP etiology differs from one ICU to another. In our series, XDR *A. baumannii* was the most common organism causing VAP, and carbapenems were the most widely used antimicrobial class. The optimum strategy for the management of VAP is a subject of research and debate. On the basis of local microbiology results and unit-specific antibiograms, as recommended by the 2016 IDSA/ATS guidelines and a profound literature search, we set an algorithm for VAP management in our ICU. Timely surveillance for resistance is an essential key for periodic review of these guidelines. In recognition of the fact that resistance can rapidly develop within a practice environment, more research is needed to determine this trend, taking into consideration prior antibiotic exposure, which has been proved to be an independent risk factor for eliminating normal flora and allowing the selection of resistant bacteria, which implies precipitating collateral damage.

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This is a retrospective study where all data were retrieved from electronic medical records and medical microbiology logbooks.

All authors have reviewed and agreed on this manuscript and authorize its publication in case of acceptance.

Disclosure

The authors report no conflicts of interest in this work.

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