Management of Ventilator-Associated Pneumonia

Emili Diaz, MD, PhD*, Marta Uldemolins, DPharm, Thiago Lisboa, MD, Jordi Rello, MD, PhD

Ventilator-associated pneumonia (VAP) management depends on the interaction between the infective agent, the host response, and the antimicrobial drug used. After the pathogen reaches the lungs, two outcomes are possible: either the microorganisms are eliminated by the host immune system, or they overcome the immune system and cause pulmonary infection. In some infectious diseases, a close relationship has been established between the outcome and the time when antibiotic therapy is started.1–3

When a patient is thought to have VAP, two steps are strongly recommended: etiologic diagnostic testing and the immediate initiation of antibiotics. Initial empiric antibiotic therapy should be based on risk factors for specific microorganisms and local epidemiology, and should then be adapted when microbiological findings are available.1,4

The microbiological results may also help physicians to narrow the spectrum of empiric antibiotics. Identification of a causative pathogen and its antibiotic susceptibility pattern allows de-escalation, that is, the strategy of starting with broad-spectrum antibiotics after obtaining microbiological tests followed by clinical and lab assessment.5 De-escalation involves three steps: (1) the collection of microbiological samples; (2) the start of empiric antibiotic therapy, bearing in mind local epidemiology and risk factors; and (3) the adaptation of the final antibiotic therapy in the light of the clinical evolution and microbiological data.

ETIOLOGIC DIAGNOSTIC TESTS

The choice of the best diagnostic test is a matter of debate. The most specific tests involved bronchoscopic samples (protected specimen brush, bronchoalveolar lavage) but nonbronchoscopic techniques, mainly tracheal aspirate, are cheaper.
Physicians’ ability to diagnose VAP is often poor, as several pulmonary diseases may present with similar clinical signs. The presence of clinical signs of pneumonia in intensive care unit (ICU) patients (fever, pulmonary infiltrates and purulent pulmonary secretion) is caused by VAP in only 30%–40% of cases. The use of quantitative cultures of respiratory samples has been advocated as a way to improve the accuracy of VAP diagnosis; however, studies to date have not demonstrated any effect on reducing antibiotic use or rates of superinfection, or any improvement in outcomes. Culture of pulmonary secretions may help to refine physicians’ clinical suspicion but must not be used alone to confirm or reject it. Microbiologic findings may help to tailor antibiotic spectra in selected patients, but they should be considered in conjunction with a reassessment of clinical response within 48–72 hours of pneumonia onset.

One currently accepted approach involves the use of the diagnostic technique available at each site and the prompt initiation of antibiotic therapy. However, when a multidrug resistant microorganism is suspected, or in case of treatment failure, a bronchoscopic approach is highly recommended. In a multinational study of 27 ICUs across Europe, Koulenti and colleagues reported that VAP diagnosis is mainly based on noninvasive procedures: from a total of 465 VAP episodes, the etiologic diagnoses were based on bronchoscopic samples in only 85 (18.3%). Diagnostic samples can help physicians with the initial empiric antibiotic treatment if Gram stain is performed; they can guide antibiotic changes and can provide the final etiology and susceptibility patterns within 24 hours.

**APPROPRIATE INITIAL EMPIRIC ANTIBIOTIC TREATMENT**

Inappropriate initial antibiotic therapy has been demonstrated to be a risk factor for mortality in nosocomial infections. Although it seems that changing antibiotics can improve the outcome, mortality remains higher than with initial adequate therapy. De-escalation is a potentially useful strategy for avoiding a high rate of inappropriate initial antibiotic therapy. Starting with broad-spectrum antibiotic coverage leads to a higher probability of correct pathogen coverage and adapting to a narrow spectrum antibiotic allows lower selection pressure.

Sandiumenge and colleagues analyzed four different antibiotic prescription strategies for VAP in a 44-month study. This study demonstrated that prescription strategies for VAP promoting antibiotic diversity were associated with a lower risk of multidrug resistant pathogen selection.

In addition to considering the effect of diversity on ecology, the initial antibiotic therapy should be based on local epidemiology and risk factors predisposing to certain agents. Soo Hoo and colleagues compared two periods in which different approaches were used to treat HAP. Based on their local epidemiology, those authors implemented a new treatment protocol emphasizing the role of empiric treatment, microbiological samples, and de-escalation. These changes achieved a higher rate of appropriate antibiotic therapy and lower mortality at 14 days, without increasing the presence of multidrug resistant microorganisms. As local susceptibility patterns may show changes over time, surveillance reports should be updated periodically, at least once a year.

Since initial empiric antibiotic treatment is a major influence on mortality, the assessment of risk factors for multidrug resistant organisms is a key point in therapy. At this point, a two-step evaluation approach should be considered. First, for early-onset VAP, it should be established whether the patient has a previous risk of presenting a multidrug resistant microorganism. Risk factors for prior acquisition of multidrug
resistant (MDR) microorganisms have been described for health care associated pneumonia,\textsuperscript{16} and for patients with VAP (Table 1);\textsuperscript{17} patient-dependent characteristics for MDR colonization differ according to the causative organism. Second, if no risk factors are present, MDR should be considered if the patient has been treated with antibiotics in the last 90 days\textsuperscript{16} or if VAP is diagnosed after 5 days of hospitalization. The cut-off point for considering a patient to be at risk for MDR is between 5\textsuperscript{16} and 7 days\textsuperscript{18} after admission. However, early-onset VAP due to MDR has also been reported in certain hospitals,\textsuperscript{19} highlighting once again the critical relevance of local epidemiology.

Another issue to be considered is MDR colonization pressure. In a prospective two-year study, Merrer and colleagues\textsuperscript{20} demonstrated that colonization pressure was the most important factor for MRSA acquisition: the higher the MRSA colonization rate in the ICU, the higher risk of MRSA acquisition by the other patients. In that study, the risk of MRSA acquisition increased fivefold when the ratio MRSA-carrier patient-days versus. the total number of patient-days was above 30%.

**PRESCRIPTION OF ANTIBIOTICS AT THE BEDSIDE**

*Combination or Monotherapy in Ventilator-Associated Pneumonia*

Empiric antimicrobial treatment choice should be patient-specific, based on risk factors and comorbidities, and individualized, considering local microbiologic

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Risk factors for VAP due to antibiotic-resistant bacteria</th>
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<tr>
<td>Health care associated methicillin-resistant <em>Staphylococcus aureus</em> (HA-MRSA)</td>
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<td>COPD</td>
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<td>Steroid therapy</td>
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<td>Longer duration of mechanical ventilation</td>
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<td>Prior antibiotic therapy</td>
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<td>Prior bronchoscopy</td>
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<td>MRSA colonization</td>
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<tr>
<td>Community-acquired methicillin-resistant <em>Staphylococcus aureus</em> (CA-MRSA) (low predictive value)</td>
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<td>Skin trauma</td>
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<td>Cosmetic body shaving</td>
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<td>Incarceration</td>
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<td><em>Pseudomonas aeruginosa</em></td>
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<td>COPD</td>
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<td>Prior antibiotic therapy</td>
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<tr>
<td>Acinetobacter baumannii</td>
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<td>ARDS</td>
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<td>Head trauma</td>
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<td>Neurosurgery</td>
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<td>Gross aspiration</td>
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<td>Prior cephalosporin therapy</td>
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Antibiotic selection in early-onset VAP without risk factors for multidrug resistant pathogens includes mostly a single narrow-spectrum agent, while in late-onset episodes the possibility of multidrug resistant organisms, and as a result a broad-spectrum treatment strategy, should be considered.

Some authors argue that a combination regimen increases the likelihood of therapeutic success through wider coverage in monomicrobial episodes of VAP and especially in polymicrobial episodes. However, some studies suggest that combination therapy may be more expensive and may be associated with greater toxicity and the emergence of multiresistant microorganisms.

Recently, Heyland and colleagues reported a randomized clinical trial comparing combination therapy (meropenem plus ciprofloxacin) versus monotherapy (only meropenem) with broad-spectrum antibiotics for suspected late VAP. They found no differences in 28-day mortality between combination and monotherapy groups, or between ICU and hospital length of stay, clinical and microbiological treatment response, or emergence of antibiotic-resistant bacteria. However, when evaluating a subgroup of patients with multidrug resistant Gram-negative bacteria, microbiological eradication of infecting organisms was significantly higher in the combination therapy group, though there were no differences in clinical outcomes. This finding may be explained by the statistically significant difference between the groups in terms of antibiotic adequacy (combination = 84.2% versus monotherapy = 18.8%). The authors’ group described similar findings in a multicenter study comparing the use of monotherapy versus combination as empiric therapy for monomicrobial VAP episodes due to Pseudomonas aeruginosa. In that study, use of combination therapy was less likely to be inappropriate than monotherapy (9.5% versus 43.3%). Nevertheless, when only appropriate therapy was considered, there was no difference in outcomes between the two treatment groups. A recent meta-analysis demonstrated that monotherapy is not inferior to combination therapy for the empiric treatment of VAP. However, the heterogeneity of the studies conducted so far limits the data quality, and further studies are necessary to clarify the issue.

In clinical practice, the choice of combination therapy in patients with a high susceptibility to multidrug-resistant pathogens such as Pseudomonas aeruginosa should take account of local microbiological data to ensure that appropriate empiric therapy is given. This approach is the key determinant of mortality risk in these patients.

Choosing the Regimen

After considering the above arguments, the physician must decide whether to start an antibiotic alone or in combination. Unless the patient is immunocompromised, antifungal therapy should be not prescribed. In early-onset VAP in patients without risk factors for MDR pathogens, therapy should be active against core pathogens (Haemophilus influenzae, Streptococcus pneumoniae and methicillin-sensitive Staphylococcus aureus). However, in patients who have VAP caused by Pseudomonas spp, Acinetobacter baumannii or extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae, the appropriateness of initial antibiotic regimen is higher with combination therapy. Options for empiric antibiotic therapy are detailed in Table 2. In patients at risk of MDR, a three-step approach is recommended (Fig. 1).

First, if there is a risk of methicillin-resistant Staphylococcus aureus (MRSA) colonization, the authors suggest linezolid as part of empiric therapy (Fig. 2). Vancomycin has been the anti-MRSA drug of choice for several years, but the mortality rate for patients with MRSA VAP treated with vancomycin has been reported to be as high as 50%. Vancomycin’s poor tissue penetration in the lung limits its ability to
optimally treat VAP episodes in spite of its in vitro appropriateness. Although no random controlled trial (RCT) comparing vancomycin versus linezolid has been designed in patients with VAP, the pooled results of two studies showed better outcomes for patients treated with linezolid compared with those treated with vancomycin. Other

| Table 2 |
| Final recommendation for antibiotic treatment in patients with VAP |

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Antibiotic Treatment</th>
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| No risk factors for MDR organisms | Amoxicillin-clavulanate  
Ampicillin-sulbactam  
Ertapenem  
Ceftriaxone |
| At risk for: Pseudomonas aeruginosa | Initial empiric antibiotic treatment  
Imipenem/cilastatin: 2 h infusion  
Meropenem: 3 h infusion  
Doripenem: 4 h infusion  
Piperacillin-tazobactam: 4 infusion  
Ceftazidime/cefepime: continuous infusion  
Combination with Ciprofloxacin |
| MRSA | Linezolid  
Vancomycin: continuous infusion to trough levels of 15–20 microg/mL |
| Acinetobacter baumannii | Carbapenem  
Sulbactam  
Colistin |
| Previously treated with antibiotic: | |
| Previous β-lactam | Carbapenem |
| Ciprofloxacin | Avoid imipenem |
| Carbapenem | Piperacillin-tazobactam |
| Aminoglycoside | Ciprofloxacin or change aminoglycoside type |

Fig. 1. Treatment decision tree for ventilator-associated pneumonia. Modified from Rello J, Diaz E. Pneumonia in the intensive care unit. Crit Care Med 2003;31:2548; with permission.
new agents with anti-MRSA activity, such as telavancin, iclaprim, ceftaroline or PZ-601, are being investigated in ongoing clinical trials. Unfortunately, most new agents (eg, daptomycin, tigecycline) have been approved for nonpulmonary indications such as abdominal or skin and soft tissue infections.

Second, if there is a risk of *Acinetobacter baumannii* colonization, carbapenem should be considered. In a case control study, patients who had VAP caused by *Acinetobacter baumannii* treated with carbapenem showed no differences in mortality compared with control patients with similar severity scores. In patients who had carbapenem-resistant strains, therapy with inhaled or intravenous colistin has been tested.

Third, if there is a risk of *Pseudomonas aeruginosa*, it has been demonstrated that at least one active agent should be present in the initial starting therapy. However, appropriate therapy is not enough. A patient-based regimen, considering issues related to the complexity of the critically ill patient and their implications for treatment is fundamental to achieving optimal management of VAP. Pharmacokinetic/pharmacodynamic (PK/PD) related concepts, such as tissue penetration, distribution volume and individualized dosing regimens in ICU practice, should be included in clinical practice to improve VAP outcome.

**Beyond Appropriateness: Pharmacokinetic-Pharmacodynamic Considerations in the Management of Ventilator-Associated Pneumonia**

In vitro susceptibility should not be the only criterion in the choice of the appropriate antibiotic. Treatment failure with an antibiotic to which the pathogen was sensitive in vitro is not uncommon.
Host factors
Critically ill patients are subject to physiologic changes that may affect the concentration achieved in both blood and peripheral tissues. Situations such as sepsis are known to increase patients’ distribution volume, producing an effect known as “third spacing,” which leads to a decrease in the blood concentration of hydrophilic drugs. This development is especially relevant in the case of antibiotics, because of the resulting probability of achieving lower concentrations than expected, thus leading to underdosing.

Moreover, renal failure is also frequent in the ICU, as the use of nephrotoxic medications such as iodine contrast or situations of hypovolemia or myocardial depression is relatively common. A decrease in the kidney filtration rate produces an inversely proportional increase in the half-life of drugs that are mainly excreted renally, leading to higher than expected drug concentrations in both plasma and peripheral tissue.

Furthermore, ventilated patients with shock usually receive fluidotherapy and/or inotropic agents as therapy to reverse the situation. The extra volume and the increase in the cardiac output leads to higher values of renal preload, which raises filtration rates and shortens drug half-life.

Albumin levels are also important, as the incidence of hypoalbuminemia is relatively high in critically ill patients. Domínguez de Villota and colleagues reported that 64% of the patients admitted to their ICU had low albumin levels. Its immediate consequence is a decrease in the colloid osmotic pressure, which in physiologic terms leads to a movement of liquid to the extravascular space, producing edema and lower than expected blood drug concentrations. Moreover, drugs can bind to plasmatic proteins in a variable percentage depending on their physicochemistry, and it is known that the unbound fraction is cleared faster. Hypoalbuminemia leads to higher free drug concentrations and may decrease drug half-life.

Antibiotic factors
An antibiotic drug’s structure has implications for its distribution, metabolism and excretion, making each antibiotic suitable for certain types of infection. Consequently, the quantitative evaluation of lung penetration is a cornerstone in the selection of the most appropriate antibiotic for treating VAP.

Time-dependent antibiotics exhibit better profiles of activity when administered in prolonged-infusion multiple-daily dosing rather than in once-daily bolus dosing. Beta-lactams, carbapenems and glycopeptides are included in this group. In contrast, concentration-dependent antibiotics, such as fluoroquinolones, aminoglycosides and macrolides, achieve better outcomes when administered in high doses once daily.

As time-dependent antibiotics, beta-lactams and carbapenems require a certain time >minimum inhibitory concentration (MIC) between doses which usually ranges between 40% and 50% in penicillins; 50%–70% in cephalosporins; and 30%–40% in carbapenems. Fast regrowth of causative bacteria has been reported.

To examine this point, several studies have compared bolus administration versus prolonged infusion, concluding that long infusions achieve better outcomes. Piperacillin-tazobactam in extended-infusion has been administered in critically ill patients infected with Pseudomonas aeruginosa, more than half of respiratory origin. In this study, 14-day mortality was lower for patients treated with extended-infusion of piperacillin-tazobactam compared with intravenous administration for 30 min every 4 or 6 hours. Doripenem, a carbapenem approved for treatment of patients with VAP, has been tested in extended-infusion. A 4-hour infusion of doripenem was not inferior to a 30- or 60-minute infusion of imipenem and exhibited better results for patients...
with higher severity as measured by APACHE II score and older age. Some reports suggest that vancomycin should be administered in continuous infusion with a trough level of 15–20 microg/mL.

Linezolid seems to follow a time-dependent profile of activity in animal models; however, in humans the best outcomes were obtained with t>MIC of 85% and AUC/MIC of 100, suggesting that its behavior is mixed.

The best outcomes with fluoroquinolones are achieved with high-dose, once-daily administrations. The study by Benko and colleagues showed that levofloxacin given to treat VAP in a schedule of 500 mg twice daily as loading dose and 500 mg once daily until the end of therapy achieved the recommended pharmacodynamic values of maximum concentration (Cmax)/MIC >10 and AUC/MIC = 100 - 150. Similar results have been reported for ciprofloxacin, confirming the dose-dependence of fluoroquinolones.

### EVALUATION OF CLINICAL RESPONSE AND ADJUSTMENT OF EMPIRIC REGIMEN

#### Clinical Resolution

In 2003, a decision tree algorithm giving full follow-up for patients with a VAP episode was published (Fig. 3). One of the key points was the clinical resolution assessment. In a clinical study of patients without acute respiratory distress syndrome (ARDS), the time to evaluate the clinical response was defined to be adequate at 48–72 hours, when around 75% of patients with good resolution exhibited an improvement in hypoxemia and fever. Clinical resolution was assessed based on the evaluation of fever, hypoxemia (measured as PaO2/FiO2 ratio), leukocyte count in peripheral blood, clearance of tracheal secretions, and opacities in chest radiograph. The most important finding was that fever and hypoxemia resolved within the first 72 hours of evolution in more than 70% of patients. The etiology comprised mainly non-difficult to treat bacteria (18.8% of Pseudomonas aeruginosa, Acinetobacter baumannii or MRSA).

A new study by the same group, focusing on the influence of microorganisms on VAP resolution, showed that the resolution of VAP by methicillin-sensitive Staphylococcus aureus, Haemophilus influenzae, and Pseudomonas aeruginosa was similar;

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**Fig. 3.** Follow-up for patients having ventilator-associated pneumonia according to microbiological results and clinical assessment. *Modified from* Rello J, Diaz E. Pneumonia in the intensive care unit. Crit Care Med 2003;31:2544–51; with permission. ATB, antibiotic therapy; ARDS, acute respiratory distress syndrome.
however, when the VAP episode was caused by MRSA the median time to resolution was 10 days.\textsuperscript{53}

In addition to clinical parameters, biomarkers have been investigated in patients who have VAP. Procalcitonin\textsuperscript{54,55} and C-reactive protein (CRP) have proved to be useful tools to assess prognosis in VAP patients.\textsuperscript{54} Moreover, a dynamic reassessment of CRP levels at day four of VAP was a marker of appropriateness and clinical response to antibiotic therapy.\textsuperscript{56}

**Changing the Empiric Regimen**

There are three ways of changing a previously prescribed antibiotic therapy: escalation to another regimen, de-escalation, or continuation of the initial antibiotic regimen. In de-escalation, treatment starts with a broad-spectrum antibiotic therapy, providing maximum coverage and minimizing the risk of inappropriate empiric treatment. When a positive culture is available, de-escalation allows the treatment to be changed to a narrow-spectrum specific therapy, minimizing the risk of emergence of resistance as the exposure to broad-spectrum agents decreases.\textsuperscript{5} Another study\textsuperscript{57} found that de-escalation was performed in 22\% of VAP episodes. The mortality rate was lower among patients in whom therapy was de-escalated compared with those without changes in therapy. The combination of clinical resolution and antibiotic susceptibility of causative microorganisms gives clinicians four options (Table 3). Without microbiological data, de-escalation is impossible by definition, because adjustment to a low antibiotic class does not guarantee correct coverage. In this situation, a) if clinical resolution is achieved, the first option is to maintain the initial antibiotic regimen. However, b) if clinical resolution of VAP is poor, the physician should consider escalating the therapy, with coverage of uncovered pathogens, and with special attention to multidrug resistant microorganisms. However, c) if microbiological results are available and VAP is likely to resolve the treatment can be modified according to the results, either maintaining the current therapy or, if possible, de-escalating. And, d) if microbiological data are present and the patient’s condition is deteriorating, the antibiotic should be modified with escalation to a broad spectrum agent, or one that covers the untreated pathogens. Finally, the entire schedule should be seen as a dynamic process in which the information is constantly updated and which considers other diagnoses such as pleural empyema, and wrong initial diagnosis. In addition, the clinical resolution pattern may differ between patients with or without ARDS.

**Antibiotic Duration**

The optimal duration of antibiotic therapy is not known. In a multicenter study performed to define the duration of antibiotic treatment, Chastre and colleagues compared 8 to 15 days of antibiotic treatment for VAP and found no difference in intent-to-treat (ITT) analysis. However, patients had longer treatment than that indicated in the protocol (17 days versus 12.5 days). In this study of patients with VAP

<table>
<thead>
<tr>
<th>Microbiological Results</th>
<th>Clinical Resolution</th>
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<tbody>
<tr>
<td>Available</td>
<td>Continue or de-escalate</td>
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<tr>
<td>Not available</td>
<td>Continue</td>
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Table 3
2 X 2 table according to empiric antibiotic therapy and availability of microbiological results
caused by nonfermentative Gram-negative bacilli, higher recurrence was seen in the
group of shorter duration.58 This higher recurrence was not observed in a retrospective
study focusing only on patients with nonfermentative bacilli.59 Other tools to decrease
the antibiotic time duration are not widely applied, although repeating bronchoalveolar
lavage has proved useful in trauma patients.60

A customized, patient-specific approach based on clinical response to antibiotic
treatment, using dynamic clinical variables and biomarkers such as CRP and proca-
laitonin (PCT), may help to optimize treatment duration. Nonetheless, this strategy is
still to be validated in prospective clinical trials.

SUMMARY

The daily management of VAP remains a challenge for physicians in the ICU. In recent
years, a more dynamic approach has evolved, updating local epidemiology, evalu-
ating VAP and diagnostic tools every day, and assessing host response using clinical
and biochemical parameters. In this situation, PK/PD properties have emerged as an
important element in antibiotic therapy.

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