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Médecine et maladies infectieuses 46 (2016) 365–371

Original article

Community-acquired pneumonia and positive urinary antigen tests: Factors associated with targeted antibiotic therapy

Pneumonies aiguës communautaires avec antigènes solubles urinaires positifs : facteurs associés à une antibiothérapie ciblée

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Received 3 December 2015; received in revised form 28 January 2016; accepted 13 May 2016
Available online 1 July 2016

Abstract

Background. – The use of rapid microbiological tests is supported by antimicrobial stewardship policies. Targeted antibiotic therapy (TAT) for community-acquired pneumonia (CAP) with positive urinary antigen test (UAT) has been associated with a favorable impact on outcome. We aimed to determine the factors associated with TAT prescription.

Patients and methods. – We conducted a retrospective multicenter study including all patients presenting with CAP and positive UAT for *Streptococcus pneumoniae* or *Legionella pneumophila* from January 2010 to December 2013. Patients presenting with aspiration pneumonia, coinfection, and neutropenia were excluded. CAP severity was assessed using the Pneumonia Severity Index (PSI). TAT was defined as the administration of amoxicillin for pneumococcal infection and either macrolides or fluoroquinolones (inactive against *S. pneumoniae*) for Legionella infection.

Results. – A total of 861 patients were included, including 687 pneumococcal infections and 174 legionellosis from eight facilities and 37 medical departments. TAT was prescribed to 273 patients (32%). Four factors were found independently associated with a lower rate of TAT: a PSI score ≥ 4 (OR 0.37), Hospital A (OR 0.41), hospitalization in the intensive care unit (OR 0.44), and cardiac comorbidities (OR 0.60). Four other factors were associated with a high rate of TAT: positive blood culture for *S. pneumoniae* (OR 2.32), Hospitals B (OR 2.34), E (OR 2.68), and H (OR 9.32).

Conclusion. – TAT in CAP with positive UAT was related to the hospitals as well as to patient characteristics.

Keywords: Community-acquired pneumonia; Urinary antigen test; *S. pneumoniae*; Legionella; Antimicrobial stewardship

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http://dx.doi.org/10.1016/j.medmal.2016.05.009
0399-077X/

Résumé

Introduction. – L'utilisation des tests rapides est recommandée pour le bon usage des antibiotiques. L'antibiothérapie ciblée des pneumonies aiguës communautaires (PAC) avec antigènes urinaires positifs (AUP) est associée à un meilleur pronostic. Notre objectif était de déterminer les facteurs associés à la prescription d'une antibiothérapie ciblée.

Patients et méthodes. – Étude multicentrique rétrospective incluant tous les patients avec une PAC, avec AUP pour le pneumocoque ou *Legionella pneumophila* (janvier 2010–décembre 2013). Les patients présentant une pneumonie d'inhalation, une co-infection ou une neutropénie étaient exclus. La gravité de la PAC était estimée par score de Fine. L'antibiothérapie ciblée était définie par l'administration d'amoxicilline pour une infection à pneumocoque ou d'un macrolide ou d'une fluoroquinolone (inactive sur le pneumocoque) dans la légionellose.

Résultats. – Au total, 861 patients inclus : 687 infections à pneumocoque et 174 légionelloses de huit établissements de santé et 37 services médicaux. Une antibiothérapie ciblée était prescrite dans 273 cas (32 %). Quatre facteurs apparaissaient reliés à un faible taux d'antibiothérapie ciblée : un score de Fine ≥ 4 (OR 0,37), l'hôpital A (OR 0,41), une hospitalisation en réanimation et une comorbidité cardiaque (OR 0,60). Quatre autres facteurs étaient associés à un taux élevé d'antibiothérapie ciblée: une hémoculture positive pour le pneumocoque (OR 2,32), les hôpitaux B (OR 2,34), E (OR 2,68) et H (OR 9,32).

Conclusion. – L'antibiothérapie ciblée dans le cadre d'une PAC documentée par AUP est fonction des établissements de santé et des caractéristiques des patients.

Mots clés : Pneumonie aiguë communautaire ; Antigènes urinaires ; Pneumocoque ; Legionella ; Bon usage des antibiotiques

Various guidelines recommend the use of an empirical antibiotic therapy including amoxicillin-clavulanic acid, third-generation cephalosporins or respiratory quinolones for community-acquired pneumonia (CAP) requiring in-hospital care. This antibiotic therapy can be qualified as having a broad antibacterial spectrum of activity [1–3].

However, the key concept in infectious disease management is microbial identification and susceptibility testing allowing for the selection of appropriate antibiotics. Accordingly, reassessing antibiotic prescriptions on Day 3 is a major goal in clinical practice for outcome improvement and for reducing the emergence of multidrug-resistant bacteria [4].

Urinary antigen tests (UAT) for *Streptococcus pneumoniae* and Legionella may be performed as part of the microbiological investigation for CAP. However, international guidelines are not unanimous regarding antibiotic reassessment in case of a positive UAT. This may be due to the non-optimal sensitivity and specificity of the test, in particular for *S. pneumoniae* [5–9].

Previous studies demonstrated that targeted antibiotic therapy (TAT) following a positive UAT could be used with no deleterious impact on clinical outcome [10–14]. We have also recently demonstrated that amoxicillin prescribed for severe CAP with positive UAT for *S. pneumoniae* was associated with a favorable outcome compared with other antibiotics [15].

Although Legionella or *S. pneumoniae* UATs have been widely prescribed over the past 15 years, their positivity rarely leads to TAT [16,17] and factors associated with TAT have not been specifically studied. We aimed to determine the factors contributing to TAT prescription based on a positive UAT for Legionella or *S. pneumoniae*.

1. Methods

1.1. Population and study design

We conducted a retrospective multicenter study including all adult patients with a positive UAT for *S. pneumoniae* or Legionella from January 2010 to December 2013.

Participating facilities are part of a profesionnal multidisciplinary network for antibiotic stewardship, which main goals are the homogenization of practices, performance of audits, and clinical researches [18–20].

Positive UATs were selected from the computerized database of the related laboratories.

The inclusion criterion was a primary discharge diagnosis of CAP in adult patients for whom a positive UAT was obtained during the study period.

Exclusion criteria were healthcare-associated infection (defined as a diagnosis established ≥ 48 hours after hospital admission), exacerbation of chronic obstructive pulmonary disease, and meningitis for which *S. pneumoniae* UAT might be positive. Also, we excluded patients whose medical records indicated aspiration pneumonia, and/or co-infection, and/or neutropenia.

Clinical data, therapeutic strategies, and outcomes were collected from patients' charts. Comorbidities were defined as the prescription of the related specific treatment before hospital admission, or during hospital stay if the diagnosis was newly established. Disease severity was evaluated using the Pneumonia Severity Index (PSI).

A positive UAT may have different impacts on antibiotic treatment prescription. If the results are immediately available, TAT may be the first course of antibiotics. If UAT results are

available after prescribing the first course of antibiotics, antibiotic reassessment may lead to TAT.

Targeted treatment was defined as the prescription of amoxicillin in case of *S. pneumoniae* infection and a macrolide or a non-respiratory fluoroquinolone (ofloxacin, ciprofloxacin) in case of Legionella infection. Thus, TAT was defined as the use of immediate targeted treatment or as antibiotic reassessment leading to targeted treatment.

Departments involved in patient management were divided into four categories: intensive care units (ICU), pneumology, infectious disease departments, and a heterogeneous group including internal medicine, geriatrics, cardiology, and gastroenterology.

1.2. Microbial investigations

All participating laboratories used the Binax-NOW® *S. pneumoniae* urinary antigen test, which was performed according to the manufacturer's instructions. UATs were performed 24 hours a day, 7 days a week in all facilities. Results were always available in less than four hours. The prescribing physician was always informed by telephone about the positivity of the result. All other bacteriological investigations were always listed, including blood cultures, respiratory specimen (regardless of the technique used: sputum, bronchoalveolar lavage, bronchial aspiration), and other microbiological samples indicative of co-infection.

1.3. Statistical analysis

Data was analyzed with the Statview software version 4.5 and statistical significance was set at $\alpha = 0.05$. Continuous variables were compared using the Mann-Whitney non-parametric test and qualitative variables were compared using the χ^2 or Fisher's exact test when appropriate. Logistic regression was used for multivariate analysis of factors associated with TAT and results were presented as adjusted odds ratios (AORs) with their 95% confidence intervals (CIs). Variables were selected as candidates for the multivariate analysis on the basis of the level of significance of the univariate association with TAT ($P < 0.1$). Models were built up sequentially, starting with the variable most strongly associated with TAT and continuing until no other variable reached significance or altered the odds ratios of variables already in the model. When the final model was reached, variable were dropped one at a time to assess their respective effect.

2. Results

Eight hospitals (one university hospital, six general hospitals, and one private clinic) participated in the study, including 37 departments: eight ICUs, five pneumology departments, two infectious disease departments, and 22 other departments (mostly internal medicine and geriatrics).

A total of 1022 CAPs with positive UATs were diagnosed, among which 161 were excluded (16% – including 11 co-infections, 36 community-acquired pneumonias complicated by healthcare-associated pneumonia, 10 patients presenting with neutropenia, and four with aspiration pneumonia). We thus included 861 patients: 687 presenting with pneumococcal infections (80%) and 174 with legionellosis.

Targeted antibiotic therapy was prescribed to 273 patients (32%). TAT was the first course of treatment for 182 of them (21%).

Table 1 shows the main antibiotic prescriptions, separately considering *S. pneumoniae* and legionellosis. Single-line treatment was more frequently used in pneumococcal infections, compared with legionellosis (< 0.001), and antibiotic reassessment leading to TAT: 33.3% in pneumococcal infections compared with 25.3% in Legionella infections ($P = 0.04$). Of note, combination therapy for legionellosis was prescribed in 45% of severe cases (PSI score ≥ 4) compared with 30% for non-severe cases ($P = 0.04$).

Fig. 1 shows that the TAT rate significantly varied between hospitals (from 0% in Hospital G to 71% in Hospital H) and departments (from 19% in ICUs to 73% in infectious disease departments). The rate of effective reassessment leading to TAT also varied between departments: 6% in pneumology departments, 10% in medical departments, 14% in infectious disease departments, and 15% in ICUs.

Patient factors associated with TAT were first studied with a univariate analysis (Table 2). Several characteristics were related to TAT, mainly cardiac comorbidities, disease severity (and therefore ICU requirement), and bacteriological results. Given that both hospital context and clinical and microbiological data had a significant impact on TAT, we performed a multivariate analysis including all of these factors. As death could not be a factor for TAT, we excluded this parameter from the multivariate analysis despite its significant association with the absence of targeted therapy in the univariate analysis.

Four factors were independently associated with a lower rate of TAT: Hospital A, hospitalization in the intensive care unit, cardiac comorbidities, and disease severity. Four other factors were associated with a high rate of TAT: Hospitals B, E, and H, and positive blood culture for *S. pneumoniae* (Table 3).

3. Discussion

Early antibiotic reassessment is a cornerstone of antimicrobial stewardship programs worldwide [4], and rapid diagnostic tests provide opportunities for therapeutic adjustment [21]. Knowledge on factors, which may influence therapeutic decision, is therefore crucial.

Our study results show that TAT in CAP with positive UAT was prescribed in 32% of cases. TAT was associated with inherent patient characteristics, such as cardiac comorbidities and disease severity as well as with extrinsic factors, namely the facility and the department where care was delivered. Our findings also corroborate previous results indicating that TAT based on positive UAT is associated with a favorable outcome [10–13,15].

This high rate of TAT, compared with previously published studies [16,17] in which such therapeutic use of positive UAT varied from 5 to 20%, may be related to differences in the definition of antibiotic reassessment [16,17,22–24]. Yet, the literature

Table 1
Main antibiotic therapies prescribed to community-acquired pneumonia patients with a positive urinary antigen test for *Streptococcus pneumoniae* and *Legionella pneumophila*.
Antibiothérapies mises en oeuvre dans le cadre de pneumonies aiguës communautaires avec antigènes solubles urinaires positifs pour Streptococcus pneumoniae *et* Legionella pneumophila.

Antibiotic therapy	*S. pneumoniae*, *n* = 687 (79.8)	*L. pneumophila*, *n* = 174 (20.2)	*P*
One course of antibiotic therapy	468 (68.1)	82 (47.1)	< 0.001
Single agent	375 (53.6)	53 (30.5)	< 0.001
Amoxillin	158 (23.0)	0	
Amoxicillin-clavulanic acid	133 (19.4)	1 (< 1%)	
Third-generation cephalosporin (Ceph-3)[a]	46 (6.7)	1 (< 1%)	
Levofloxacin	34 (4.9)	27 (15.5)	
Macrolide[b]	2 (< 1%)	16 (9.2)	
Other fluoroquinolones[c]	2 (< 1%)	8 (4.6)	
Main antibiotic combinations (unchanged)	93 (13.5)	29 (17.2)	0.212
Ceph-3 + levofloxacin	41 (6.0)	4 (2.3)	
Ceph-3 + macrolide	9 (1.3)	2 (1.1)	
Levofloxacin + macrolide	0	13 (7.5)	
Amoxicillin-clavulanic acid + levofloxacin	15 (2.2)	1 (<)	
Other	28 (4.0)	9 (5.7)	
Antibiotic reassessments (2 courses)	182 (26.5)	74 (42.5)	< 0.001
Leading to antibiotic with a narrower spectrum[d]	102 (14.8)	32 (18.4)	
	71 (10.4)	20 (11.5)	
Leading to targeted therapy	9 (1.3)	22 (12.6)	0.001
Other	37 (5.4)	18 (10.3)	0.016
≥ 3 courses of antibiotics			

[a] Cefotaxime, ceftriaxone, ceftazidime.
[b] Erythromycin, roxithromycin, spiramycin, clarithromycin.
[c] Ciprofloxacin, ofloxacin.
[d] A narrower spectrum of activity was defined as the withdrawal of one agent from a combination therapy or the modified prescription using an agent with a narrower antibacterial spectrum of activity.

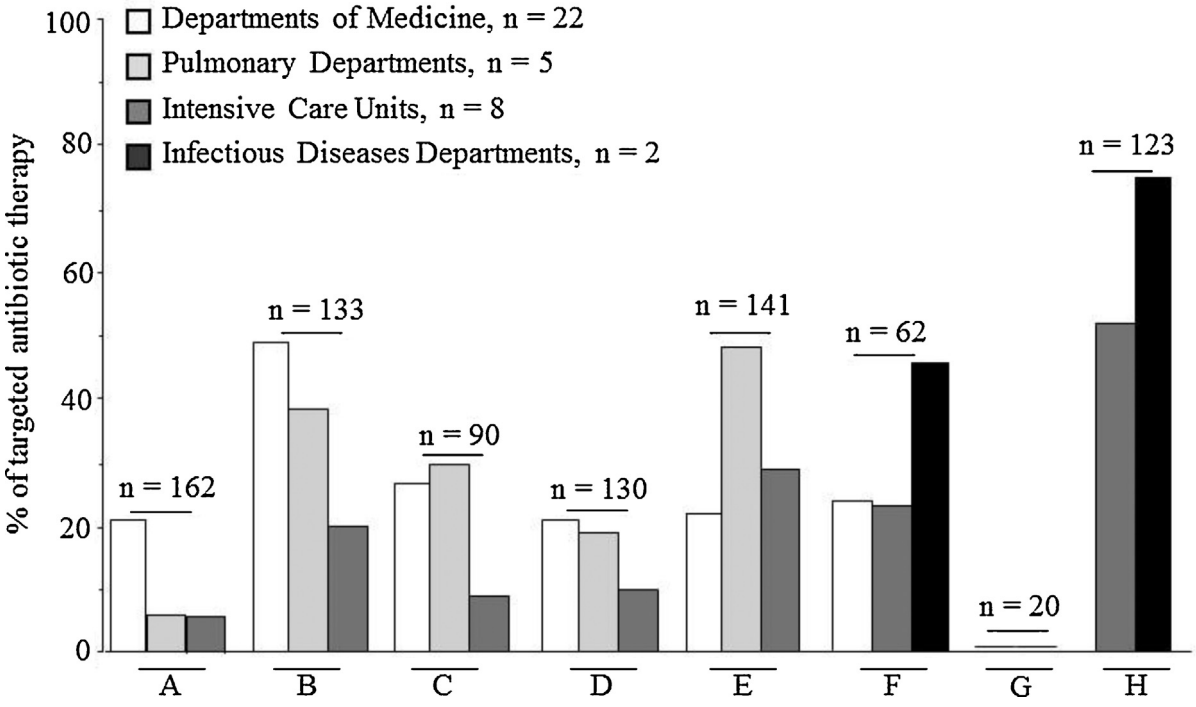

Fig. 1. Rate of targeted antibiotic therapy in eight healthcare facilities according to four medical specialties. Medicine departments included internal medicine, geriatrics, cardiology, and gastroenterology departments. The number of patients is indicated for each facility. One intensive care unit and one medical department were included in facility G.
Taux d'antibiothérapie ciblée dans huit établissements de santé selon quatre spécialités médicales.

Table 2
Factors associated with targeted antibiotic therapy for community-acquired pneumonia with positive urinary antigen test for *Streptococcus pneumoniae* or *Legionella pneumophila* (univariate analysis).
Facteurs associés à une antibiothérapie ciblée dans les pneumonies aiguës communautaires avec antigènes solubles urinaires positifs pour Streptococcus pneumoniae *ou pour* Legionella pneumophila *(analyse univariée).*

	TAT, $n = 273$ (31.7)	No TAT, $n = 588$ (68.3)	P
Age (years, mean ± SD)	64 ± 19	72 ± 17	< 0.001
Sex-ratio (M/F)	1.14	1.30	0.386
ICU requirement	47 (17.2)	193 (32.8)	< 0.001
Comorbidities			
Penicillin allergy	4 (1.5)	20 (3.4)	0.108
Cardiovascular	101 (37.0)	322 (54.8)	< 0.001
Chronic heart failure	7 (2.6)	36 (6.1)	0.026
Diabetes	28 (10.2)	77 (13.1)	0.236
Neurological and/or psychiatric	49 (17.9)	128 (21.8)	0.197
Pulmonary	84 (30.8)	206 (35.0)	0.218
COPD	33 (12.1)	119 (20.2)	0.003
Active smoking	56 (20.5)	131 (22.3)	0.559
Cancer/immunosuppression	23 (8.4)	91 (15.5)	0.004
HIV infection	22 (8.0)	10 (1.7)	< 0.001
Alcohol abuse	26 (9.5)	48 (8.2)	0.507
Liver diseases	21 (7.7)	37 (6.3)	0.446
Chronic renal failure	12 (4.4)	36 (6.1)	0.304
PSI score (n = 748, 87%)	88 ± 37	110 ± 37	< 0.001
PSI < 3	84 (38.2)	67 (12.7)	< 0.001
PSI 3	44 (20.0)	96 (18.2)	0.561
PSI 4	62 (28.2)	219 (41.5)	< 0.006
PSI 5	30 (13.6)	146 (27.6)	< 0.001
Microbial data			
S. pneumoniae	229 (83.8)	458 (77.9)	0.042
L. pneumophila	44 (16.1)	130 (22.1)	0.042
Blood culture performed	219 (80.2)	431 (73.3)	0.028
Positive for *S. pneumoniae*	37 (13.7)	47 (8.1)	0.010
S. pneumoniae isolation	78 (28.6)	82 (13.9)	< 0.001
L. pneumophila isolation	19 (7.0)	19 (3.2)	0.013
Duration of hospital stay[a]	9 [1–154]	12 [1–193]	< 0.001
Death	7 (2.6)	91 (15.5)	< 0.001

TAT: targeted antibiotic therapy; COPD: chronic obstructive pulmonary disease; PSI: Pneumonia Severity Index.
[a] Days, median [range].

Table 3
Risk factors for targeted antibiotic therapy in patients presenting with community-acquired pneumonia with positive urinary antigen test for *Streptococcus pneumoniae* or *Legionella pneumophila* using a stepwise logistic regression analysis.
Facteurs associés à une antibiothérapie ciblée dans les pneumonies aiguës communautaires avec antigènes solubles urinaires positifs pour Streptococcus pneumoniae *ou pour* Legionella pneumophila *(analyse multivariée par régression logistique).*

Risk factors	P-value	AOR [95% CI]
Hospital A	0.013	0.41 [0.21–0.83]
Hospital B	0.001	2.34 [1.40–3.89]
Hospital E	< 0.001	2.68 [1.66–4.33]
Hospital H	< 0.001	9.74 [5.25–18.07]
Intensive care unit requirement	< 0.001	0.44 [0.28–0.70]
PSI < 3	< 0.001	2.65 [1.81–3.87]
Cardiac comorbidities	0.007	0.60 [0.41–0.87]
Blood culture positive for *S. pneumoniae*	< 0.001	2.27 [1.26–4.07]

AOR: adjusted odds ratio; PSI: Pneumonia Severity Index.

rate of antibiotic modification based on microbiological investigations for CAP varies from 1 to 36% for respiratory samples or blood cultures [25–27]. These results indicate that therapeutic guidelines must describe with precision the best way to adjust the antibiotic therapy on the basis of repeated microbiological data.

We observed a significant variability in the rate of TAT between hospitals and medical specialties. Among possible explanatory factors, the delay for UAT results was comparable between healthcare facilities and cannot account for a difference in therapeutic practices. Moreover, the number of residents was similar in the various participating departments. With the exception of Hospital H, all patients benefited from computerized prescription during the study period. Two out of eight facilities (C and H) had a protocol that specified the therapeutic strategy to adopt with CAP patients with a positive UAT. Accordingly, several studies demonstrated the favorable impact

of an internal guideline on antibiotic reassessment leading to targeted antibiotic therapy [24,28,29].

Hospitalization site was a key factor for TAT in the context of CAP: patients hospitalized in Hospital H were 9.7 times more likely to receive targeted therapy. This might be explained by a higher awareness of the national antibiotic stewardship policy, which includes the use of rapid bacteriological tests and antibiotic reassessment [24,30]. Also, none of the two hospitals with the lowest rates of TAT had an infectious disease department (Fig. 1). Although each facility had a lead antibiotic specialist, his/her specialty varied. This implies inevitable disparities in dedicated timework. Consequently, antibiotic therapy advice seemed to be uneven between hospitals.

TAT related to positive UAT was associated with specific patient characteristics. Our study findings highlight fewer TAT prescriptions to patients presenting with cardiac comorbidities. Physicians providing infectious disease advice are often confronted with the following misinterpretation: if severe comorbidities such as chronic heart failure can be associated with a worse outcome in pulmonary diseases, it is however not associated with variable predictive value of UAT results.

Furthermore, a high PSI score as well as hospitalization in the ICU were associated with fewer TAT prescriptions, highlighting the absence of consensual consideration for UAT results in guidelines [1–3]. However, as indicated above, ICU physicians were prompted to perform antibiotic reassessment leading to TAT. They are indeed confronted to multidrug-resistant bacteria in the context of healthcare-associated infections and therefore pratice antibiotic de-escalation [30]. Lastly, pneumococcal bacteremia was associated with TAT. This finding is in line with the high rate of TAT reported in the present study.

4. Conclusion

Our study results show that, in real life, TAT is associated with several independent factors: the hospital itself, in which medical practices vary along with physician specialties, patient characteristics, and microbiological results. This information should be considered for antimicrobial stewardship perspectives, driving the improvement of clinical practices through a multidisciplinary network.

Authors contribution

Anaïs Mothes, Pierre-Marie Roger, Aurélie Smets, and David Chirio designed the study, collected part of the data, performed the statistical analysis, and wrote the article.

Sophie Léotard, Isabelle Nicolle, Christine Rotomondo, Fabrice Tiger, Pascal Del Giudice, Christophe Perrin, Dominique Néri, Cédric Foucault, Marc Della Guardia, and Hervé Hyvernat collected data.

Funding

No funding has been received to perform this study.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgement

The authors would like to thank other contributors: Draguignan Hospital: A. Zumbo, Bacteriology Lab, C. Labat, Pharmacy, P. Brofferio, Intensive Care Unit, E. Harb, Pneumology Department; Cannes Hospital: N. Montagne, Internal Medicine, P.M. Bertrand, Intensive Care Unit; Antibes Hospital: O. Raguin, Intensive Care Unit, L. Lerousseau, Pneumology Department; Hyères Hospital: S. Chadapaud, Infectious Disease Department. Fréjus-St-Raphael Hospital: B. Desurmond, Pneumology Department, M. Kaidomar, Intensive Care Unit, J. Gutnecht, Internal Medicine.

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