

Using procalcitonin (PCT) to guide antibiotics escalation in suspicious infected patients: a new application of PCT in ICU

Xu Wang

Peking Union Medical College Hospital

Huaiwu He

Peking Union Medical College Hospital

Yun Long (✉ ly_wxicu@163.com)

Peking Union Medical College Hospital

Guangliang Shan

Peking Union Medical College Hospital

Dongkai Li

Peking Union Medical College Hospital

Xiang Zhou

Peking Union Medical College Hospital

Longxiang Su

Peking Union Medical College Hospital

Qing Zhang

Peking Union Medical College Hospital

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Abstract

Background Empirical antibiotic therapy before pathogen recognition is a tricky problem for suspicious infected patients in ICU. Procalcitonin (PCT) is efficient in degrading antibiotics level without increasing complications for its sensitivity and specificity in bacterial infection. Considering this, we hypothesized that PCT might be significant in indicating timely antibiotics escalation and improve patients' outcomes.

Methods This was a single-center retrospective study including patients with suspected infection who were admitted to Peking Union Medical College Hospital from January 2014 to June 2018. Patients were labelled as "antibiotic escalation" or "non-escalation" according to their antimicrobial use 48 h before and after the "PCT alert". "PCT alert" was defined as PCT ≥ 1.0 ng/mL that had not decreased by at least 10% from the previous day or from baseline, or a single measurement ≥ 1.0 ng/ml. Indicators that possibly influenced the prognosis were collected. 28-day intensive care unit (ICU)-free days were calculated; ICU stays >20 days and ≤ 20 days were considered nonprolonged ICU stays (nPISs) and prolonged ICU stays (PISs), respectively. Difference analysis and binary logistic regression were performed to determine the factors that influenced the 28-day ICU-free days .

Results A total of 1109 patients were included, 654 in the PIS group, other 455 in nPIS group. The PIS group had higher rates of pathogen identification (33.94% vs 28.13%, $P=0.047$) and escalated antibiotic therapy (35.47% vs 20.66%, $P<0.001$) but a lower proportion of surgical patients (39.45% vs 54.95%, $P<0.001$) than the nPIS group. Regarding PCT, the values on the 1st day (20.36 ± 43.89 vs 14.89 ± 30.37 ug/L, $P=0.014$) and on the "alert day" (24.24 ± 46.38 vs 18.75 ± 32.69 ug/L; $P=0.021$) were higher in the PIS group than nPIS group, but no significant difference in the white blood cell (WBC) count was revealed. According to the binary logistic regression model, antibiotic escalation (OR=0.552, 95% CI 0.347-0.877, $P=0.012$) was a negative factor for PIS, while postsurgical status (OR=1.959, 95% CI 1.269-3.023, $P=0.002$) and age (OR=1.020, 95% CI 1.007-1.034, $P=0.003$) were positive factors.

Conclusions PCT is significant in evaluating the effect of empirical antibiotic therapy. Escalating microbial ranks when "alert PCT" appeared can increase 28-day ICU-free days.

Backgrounds

The level of procalcitonin (PCT) is regarded as an indicator of bacterial infection[1]. Many studies have confirmed that PCT-guided antibiotic de-escalation can decrease the duration and dose of antibiotics without increasing the risk of adverse events[2–5]. The reason why PCT is useful in assisting modifying antibiotic application for bacterial infection is mainly for its specificity and sensitivity in recognizing inflammation induced by germ[6]. We can degrade antibiotic level if PCT decreases as expected or reach a certain value[2–5], but if the PCT doesn't decrease dramatically or even increase, can we say it indicating we should escalate the ranks of anti-bacterial drugs? So far, not so many studies on this topic.

Broad-spectrum antibiotics are recommended for critically infected patients before pathogenic identification as an empirical treatment[7]. For this group of patients, adjusting antimicrobial application without pathogen evidence is challenging. On top of that, the proportion of drug-resistant bacteria is much higher in the intensive care unit (ICU) than that in general wards[8]. It's hard to decide whether to upgrade antibiotics or not for infected patients in ICU if PCT shows no sign of reduction. However,

escalating antibiotics on the basis of only increased PCT is not recommended by some guidelines and research[9, 10], as it may result in the overuse of antibiotics without outcome improvements. But previous trials were randomized controlled trials (RCTs) and did not conform to the double-blinded principle.

Considering the property of PCT, we inferred that unsatisfactory decline of PCT indicating uncontrolled infection. If we have no evidence of pathogen to refer to, empirical antibiotic escalation might be beneficial to patients. This study was performed to prove our assumption.

Patients And Methods

Patients

The Institutional Research and Ethics Committee of the Peking Union Medical College Hospital approved this study. Written informed consent was waived since it was a retrospective study.

This was a retrospective study of suspected infection patients admitted to the Department of Critical Care Medicine in Peking Union Medical College Hospital (Beijing, China) from January 2014 to June 2018. The inclusion criteria was as follows: a. patients were ≥ 18 years old; b. patients had a length of ICU stay (LOS ICU) > 24 h; c. patients had suspected infection, were administered antibiotics and received a body fluid culture (such as blood, sputum, ascitic fluid, hydrothorax, drainage fluid, etc.); and d. patients experienced a “PCT alert” during their ICU stay. We excluded patients who were discharged against medical advice, patients who died.

Data collection

The medical records of all the recruited patients were examined to collect information on sex, age, surgery (yes or no), duration of MV, LOS ICU, PCT level, WBC count, maximum daily temperature (Tmax), lactate level, dose of NE ($> 0\text{ug kg}^{-1} \text{min}^{-1}$), SOFA score, pathogen identification, and antibiotics. For the indicators (PCT, WBC, Tmax, lactate level, dose of NE, SOFA score), we collected data from only two days (1st day as baseline and the “PCT alert” day). Our department has an advanced monitoring system that records real-time clinical data from bedside equipment and laboratory examination results. This system is maintained by the Donghua software cooperation through the DtHealth system.

The 28-day ICU-free day values were calculated as 28 minus the LOS ICU; the 28-day MV-free day values were calculated similarly. The values of the 28-day ICU-/MV-free days in patients who survived or required ventilation longer than 28 days or died within 28 days were regarded as zero. The mean arterial pressure (MAP) was not included in this study because in our department, we correct blood pressure that is lower than normal with vasopressors; this, patients probably had normal blood pressure despite their different illnesses.

In addition to the detailed antibiotic information, data from 48 h before and after the “PCT alert” day were also collected.

Definitions

A “PCT alert” was defined as a PCT level ≥ 1.0 ng/mL that had not decreased at least 10% from the previous day or from baseline, or a single PCT measurement ≥ 1.0 ng/mL[9].

We referred to a document which was released by Beijing Municipal Health Commission about antibiotic management in Beijing, China. An additional file shows this document in more detail [see Additional file 1]. In that document, every antibiotics was labelled as “no restriction”, “restriction” or “only under very special condition” according to their property. “No restriction” means the antimicrobial covers most of the common bacteria without evident sideeffect. We regarded this group as the lowest grade. “Only under very special condition” indicates very strict rules for its super antimicrobial property, which is more likely to induce drug resistance. Besides, these antibiotics have more serious sideeffects. We considered this group as the highest level. Published research articles [11] were another referential resource. Besides, in our department, a group of physicians, including 4 residents, 4 attending doctors, 2 senior doctors and 2 professors held a meeting to finally come up with the grades of each type of antibiotic (Fig. 1).

With the aim of determining the influence of antibiotic escalation after a “PCT alert”, we first defined “escalation” and “nonescalation”. The main types of antimicrobials in our hospital were divided into 2 groups according to their antibacterial spectrum: G + and G-. Information on antibiotic administration 48 h before and after the “PCT alert” was analyzed. “Escalation” was defined as 1) the maximum grades in both groups were escalated; 2) the maximum grade in one group was escalated, while the grade in the other group remained unchanged or was deescalated; or 3) the maximum grades in both groups were unchanged, but the overall types of antibiotics increased. It is worth noting that patients for whom the maximum grades in both groups remained unchanged or were deescalated but the overall types in either group were increased were not included in the escalation group. The patients who were not included in the “escalation group” were included in the “nonescalation” group.

Statistical analysis

Descriptive analyses were performed for the nonescalation and escalation groups. Continuous variables are expressed as means \pm standard deviations, and categorical variables are expressed as absolute values and percentages. For the continuous variables, the data were analyzed using Student’s t-test, the Mann-Whitney U test or the Kruskal-Wallis test depending on the data distribution and the number of variables. The categorical variables were analyzed using chi-square or Fisher’s exact tests.

Patients who stay longer than 7 days in the ICU are more likely to have complications such as ventilator-associated pneumonia, ICU-acquired weakness, and high long-term mortality[12–14]. Therefore, in our study, those with 28-day ICU-free days > 20 days were considered the nonprolonged ICU stay (nPIS) group. The parameters between the two groups were compared.

A multivariable binary logistic regression model was built to determine the factors associated with an nPIS. Indicators on the “PCT alert” day, baseline data and demographic factors were included in the

model. All comparisons were two-tailed, and $P < 0.05$ was required to exclude the null hypothesis. The statistical analyses were performed using IBM SPSS Statistics, Version 20.0 (Armonk, NY: IBM Corp.).

Results

Participants

During our study period, 8672 patients were admitted to our department. A total of 7563 patients were excluded for the following reasons: 481 were younger than 18 years old; 1985 were discharged from the ICU within 24 h; 1749 did not receive antibiotics; 2533 did not have a culture performed; 649 did not present a “PCT alert”; and 166 were discharged against medical advice. Finally, 1109 patients were included. The flow diagram for patient enrollment is shown in Fig. 2. Among these 1109 patients, 654 were included in the PIS group, while 455 were included in the nPIS group.

Descriptive and outcome data

The PIS group had less 28-day ICU-free days (12.85 ± 6.72 vs 22.60 ± 1.10 days, $P < 0.001$) and MV-free days (13.85 ± 6.98 vs 23.71 ± 1.13 , $P < 0.001$) than the nPIS group. Regarding the demographic characteristics, the PIS group had lower proportions of patients who underwent surgery (39.45% vs 54.95%, $P < 0.001$) and female patients (34.10% vs 41.10%, $P = 0.021$), but the patients were significantly older than those in the nPIS group (58.99 ± 16.11 years vs 56.11 ± 16.47 years, $P = 0.004$). The PIS group had higher rates of pathogen identification (33.94% vs 28.13%, $P = 0.047$), escalated antibiotic therapy (35.47% vs 20.66%, $P < 0.001$) and mortality (6.57% vs 3.08%, $P = 0.014$) than the nPIS group.

Regarding infection indicators, we did not observe significant differences in the WBC counts or lactate levels on the 2 days between the two groups. The Tmax on the 1st day was higher in the nPIS group than in the PIS group ($37.76 \pm 0.84^\circ\text{C}$ vs $37.94 \pm 0.78^\circ\text{C}$). However, the PCT values on the 1st day (20.36 ± 43.89 vs 14.89 ± 30.37 ug/L, $P = 0.014$) and on the “alert day” (24.24 ± 46.38 vs 18.75 ± 32.69 ug/L; $P = 0.021$) were higher in the PIS group than in the nPIS group. The SOFA scores (1st day: 11.16 ± 3.57 vs 9.73 ± 3.54 , $P < 0.001$; alert day: 10.97 ± 3.76 vs 9.23 ± 3.99 , $P < 0.001$) showed the same tendency. The P/F ratio was lower in the PIS group than in the nPIS group (1st day: 284.62 ± 137.85 vs 315.67 ± 139.99 , $P = 0.003$; alert day: 291.83 ± 152.91 vs 322.04 ± 139.32 , $P = 0.011$).

The application of NE was regarded as evidence reflecting potential infection, and the proportion of people treated with NE was higher in the PIS group than in the nPIS group on both days (1st day: 75.84% vs 67.91%, $P = 0.004$; alert day: 75.69% vs 59.78%, $P < 0.001$).

Main results

In the binary logistic regression model, antibiotic escalation (OR = 0.552, 95% CI 0.347–0.877, $P = 0.012$) was a negative factor for PIS, while postsurgical status (OR = 1.959, 95% CI 1.269–3.023, $P = 0.002$) and age (OR = 1.020, 95% CI 1.007–1.034, $P = 0.003$) were positive factors. Other factors, such as WBC count, SOFA score, lactate level, etc., were not significantly associated with PIS (Table 2).

Table 1

		Prolonged N = 654	Nonprolonged N = 455	P
28-day ICU-free days		12.85 ± 6.72	22.60 ± 1.10	< 0.001
28-day MV-free days		13.85 ± 6.98	23.71 ± 1.13	< 0.001
Age (years)		58.99 ± 16.11	56.11 ± 16.47	0.004
Sex F/%		223/34.10%	187/41.10%	0.021
Surgery n/%		258/39.45%	250/54.95%	< 0.001
PCT ug/L	1st day	20.36 ± 43.89	14.89 ± 30.37	0.014
	Alert day*	24.24 ± 46.38	18.75 ± 32.69	0.021
WBC count *10 ⁹ /L	1st day	14.64 ± 8.72	14.69 ± 7.97	0.924
	Alert day	14.63 ± 8.90	13.94 ± 7.91	0.199
P/F ratio	1st day	284.62 ± 137.85	315.67 ± 139.99	0.003
	Alert day	291.83 ± 152.91	322.04 ± 139.32	0.011
Lactate mmol.L ⁻¹	1st day	3.14 ± 3.29	3.02 ± 3.11	0.656
	Alert day	2.99 ± 3.26	2.81 ± 3.15	0.499
Tmax °C	1st day	37.76 ± 0.84	37.94 ± 0.78	< 0.001
	Alert day	37.73 ± 0.80	37.80 ± 0.79	0.167
SOFA	1st day	11.16 ± 3.57	9.73 ± 3.54	< 0.001
	Alert day	10.97 ± 3.76	9.23 ± 3.99	< 0.001
NE > 0 ug/kg ⁻¹ .min ⁻¹ n/%	1st day	496/75.84%	309/67.91%	0.004
	Alert day	495/75.69%	272/59.78%	< 0.001
Escalated n/%		232/35.47%	94/20.66%	< 0.001
EOP** n/%		222/33.94%	128/28.13%	0.047
PCT: Procalcitonin; Alert day: the day of the "PCT alert"; WBC: white blood cell count; P/F ratio: PaO ₂ /FiO ₂ ; Tmax: the maximum body temperature on one day; SOFA: systematic organ function assessment; NE: norepinephrine; EOP: evidence of pathogen.				

Table 2

Variable	B	Wald	P	OR	95% CI for OR	
					Lower	Upper
Multivariate						
Surgery	0.672	9.212	0.002	1.959	1.269	3.023
Sex	0.234	1.153	0.283	1.263	0.824	1.936
Age	0.020	8.578	0.003	1.020	1.007	1.034
WBC count*	-0.069	1.575	0.210	0.933	0.837	1.040
Tmax*	-0.391	1.675	0.196	0.676	0.374	1.223
SOFA score*	0.045	0.226	0.634	1.046	0.868	1.260
PCT*	-0.007	0.752	0.386	0.993	0.978	1.009
P/F ratio*	-0.001	0.071	0.790	0.999	0.995	1.004
NE* > 0 ug/kg ⁻¹ .min ⁻¹	-0.729	0.863	0.353	0.482	0.104	2.246
EOP+	0.206	0.771	0.380	1.229	0.776	1.946
Escalating antibiotics	-0.595	6.321	0.012	0.552	0.347	0.877
SOFA 1st	0.106	1.284	0.257	1.112	0.925	1.337
PCT 1st	0.011	1.661	0.197	1.011	0.995	1.027
WBC count 1st	-0.069	1.575	0.210	0.933	0.837	1.040
P/F ratio 1st	0.000	0.005	0.944	1.000	0.996	1.004
Lactate 1st	0.090	0.890	0.345	1.094	0.908	1.319
Tmax 1st	-0.391	1.675	0.196	0.676	0.374	1.223
NE > 0 ug/kg ⁻¹ .min ⁻¹ 1st	0.823	1.124	0.289	2.278	0.497	10.438
CI: confidence interval; PCT: Procalcitonin; Alert day: the day of the "PCT alert"; WBC: white blood cell; P/F ratio: PaO ₂ /FiO ₂ ; Tmax: the maximum body temperature on one day; SOFA: systematic organ function assessment; NE: norepinephrine; EOP: evidence of pathogen.						

Discussion

The most important finding of our study was that the timely escalation of antibiotics after the PCT reached an "alert" level was beneficial for those in the nPIS group, which contradicts previous

conclusions. In addition, this is the first real-world PCT research in China.

PCT has been widely recognized as an indicator of bacterial infection for a long time, and many high-quality studies have demonstrated its significance in guiding antibiotic applications. Most studies focused on when to initiate or stop antimicrobial drugs in patients with infection. However, in the real-world clinical environment, physicians tend to be more cautious, especially regarding critically ill patients or patients at high risk for drug resistance.

Andreas Hohn et al.[5] reported low adherence to a PCT-guided antibiotic treatment protocol in real-world clinical situations involving high-risk sepsis patients if they had insufficiently decreasing or even increasing PCT. This result might reflect the significance of PCT in the real world, which is why we performed this study in a real-world clinical environment, unlike previous studies[9]; we found that the timely escalation of antibiotics when the PCT level does not decrease as expected is a negative factor for PISs (28-day ICU-free days \leq 20 days). This important finding leads us to hypothesize that a “PCT alert” might remind medical staff of the high possibility of multidrug resistant germs and that escalating drug grades might improve the outcomes of patients.

Jensen et al.[9] proved that antimicrobial spectrum escalation guided by PCT prolonged the patients’ ICU stays and increased the possibility of organ-related harm. However, there was an important inherent design flaw in this study; the physicians were not double-blinded to the PCT values, which may have led to bias because physicians tend to be “overcautious” if they are alerted to an abnormal PCT level. This means that physicians’ decisions regarding transfer or extubation may have been unfairly influenced in the “PCT intervention” group[15].

In our study, PCT tests were performed, and the results were informed, which eliminated bias. To rectify the influence of a patients’ baseline condition, we included their baseline information (sex; age; surgery; and the SOFA score, PCT level, Tmax, lactate level, and the P/F ratio on the 1st day after ICU admission) in the binary logistic regression model. The two designs and data analysis methods made the results more reliable.

In the real world, doctors tend to be more scrupulous in adjusting antibacterial drugs, especially for patients in the ICU. It is not only because of the illness but also because of the increased possibility of bacterial drug resistance in ICUs. Peking Union Medical College Hospital is a very renowned hospital in China, with the responsibility of treating complicated and serious diseases, especially those requiring ICU admission. Many of our patients are transferred from other hospitals and have long-term antimicrobial application histories. Therefore, the proportion of multidrug resistant bacteria is increased.

Understandably, our physicians tend to escalate antibiotics when patients with infection do not present obvious recovery or present characteristics such as a “PCT alert” after the application of broad-spectrum antibiotics. However, it should be noted that our conclusion might be biased because it is suited to only a certain group of patients. Applying this conclusion practically and scientifically requires further investigation. Despite the bias, a “PCT alert” is still important for informing doctors of uncontrolled infection and the potential necessity of antimicrobial escalation.

In addition to the above findings, we also found that surgical patients tended to have longer ICU stays than patients without surgery, but PIS patients had a lower proportion of surgery than nPIS patients. Our department is a surgical ICU ward, and patients admitted to our department for surgery usually have less severe health conditions than patients who are admitted for nonsurgical reasons. Nonsurgical patients tend to stay longer in the ICU than surgical patients. Surgical site infections (SSIs) account for a large proportion of healthcare-associated infections, which means that surgery could be a risk factor for infection[16–18]. Surgical patients who are transferred to the ICU are more likely to have nosocomial infections than surgical patients in non-ICU wards[19]. All of the above factors might influence patients' ICU stays. Therefore, we analyzed the influential variables by building a binary logistic regression model and found that surgery was an independent risk factor for delayed ICU discharge.

Our study is the first to focus on escalating antimicrobials in a real-world environment, and the results are very novel. To determine what to do in the face of a “PCT alert”, we analyzed only the indicators on the alert day along with baseline and demographic characteristics. There were some limitations to our study. First, it was a single-center retrospective study, and considering our hospital's specificity, our conclusion on escalating antibiotics according to a “PCT alert” might be restricted to serious patients receiving long-term treatment or hospitals with a high proportion of multi-resistant bacteria. Despite this possible limitation, an unexpected decrease in the PCT level should be regarded as a warning signal for doctors. Second, the patients were very heterogeneous. To reflect real clinical conditions, we did not establish very strict inclusion criteria. This may have led to some deviations and counteracted some of the significance. Therefore, it would be better to further divide the groups into subgroups to analyze the data in depth. However, because of the limited sample size, the number of patients in some of the subgroups would have been very small, affecting the analysis. We should collect more data to perform subgroup analyses in the future. Third, the definition of nPIS and PIS may have been a too arbitrary. However, for most ICU patients, an ICU stay longer than 7 days increases the possibility of complications and indicates poor outcomes. Therefore, we used “28-day ICU-free days > 20” as the cutoff value to distinguish patients with relatively short ICU-free days and thus worse prognoses. This value might be slightly increased for all ICU patients because this particular group of patients accounted for less than 30% of the patients in our department. Fourth, despite our large total sample size, as a retrospective study, missing data was inevitable.

Conclusions

An unexpected decrease in PCT in patients being treated with long-term broad-spectrum antibiotics indicates an increased possibility of infection with multidrug resistant bacteria; the timely escalation of antimicrobial grades may improve patients' outcomes.

List Of Abbreviations

PCT :procalcitonin; ICU: intensive care unit; nPISs: nonprolonged ICU stays; PISs: prolonged ICU stays; WBC: white blood; OR: odds ratio; CI: confidence interval; G+: gram-positive; G-: gram-negative; RCTs:

randomized controlled trials; LOS ICU: length of ICU stay; MV: mechanical ventilation; Tmax: maximum daily temperature; NE: norepinephrine; SOFA: Sequential Organ Failure Assessment.

Declarations

Ethics approval and consent to participate

The Institutional Research and Ethics Committee of the Peking Union Medical College Hospital approved this study for human subjects. Because this retrospective study only collected clinical data, the Institutional Research and Ethics Committee waived the need to obtain consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due the security of our patients, but are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

YL conceived and designed the study, interpreted data and helped draft the manuscript. XW and HH participated in the study conception and design, recruited patients, collected data, performed the statistical analysis, interpreted the data and drafted the manuscript. DL and QZ participated in technically support and data collection. XZ and LS contributed in the critical review of the manuscript. participated in data collection. GS assisted us in performing the statistical analysis. All authors read and approved the final manuscript.

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Supplementary File Legend

Additional file 1:

This is a file describing the general classification of different antimicrobials released by Beijing Municipal Health Commission in order to manage antibiotic application in hospital. In this document, every antibiotics was labelled as “no restriction”, “restriction” or “only under very special condition” according to their property. “No restriction” means every doctor has right to prescribe the drugs. “Restriction” implicates only superior doctors have the prescriptive right of the drugs. “Only under very special condition” indicates doctors have to ask for instructions from the head of department to prescribe these drugs, giving adequate reasons for his/her medical decisions.

Figures



	G+	G-
	—	Tigecycline
	Tigecycline	Imipenem
	Linezolid Teicoplanin	Meropenem
	Daptomycin	Ertapenem
	Vancomycin	Aminoglycosides
	Fourth-generation Cephalosporins Cephalosporins or Penicillin+Beta-lactamase inhibitors	Fourth-generation Cephalosporins Cephalosporins or Penicillin+Beta-lactamase inhibitors
	Third-generation Cephalosporins	Third-generation Cephalosporins
	Fluoroquinolones	Fluoroquinolones
	Cephamycin Second-generation Cephalosporins	Cephamycin Second-generation Cephalosporins

Figure 2

Antibiotic Hierarchy from the Most-Broad-Spectrum (Top) to Least-Broad-Spectrum (Bottom) Antibiotic
 G+: Gram-positive Organism Antibiotic Algorithm; G-: Gram-negative Organism Antibiotic Algorithm

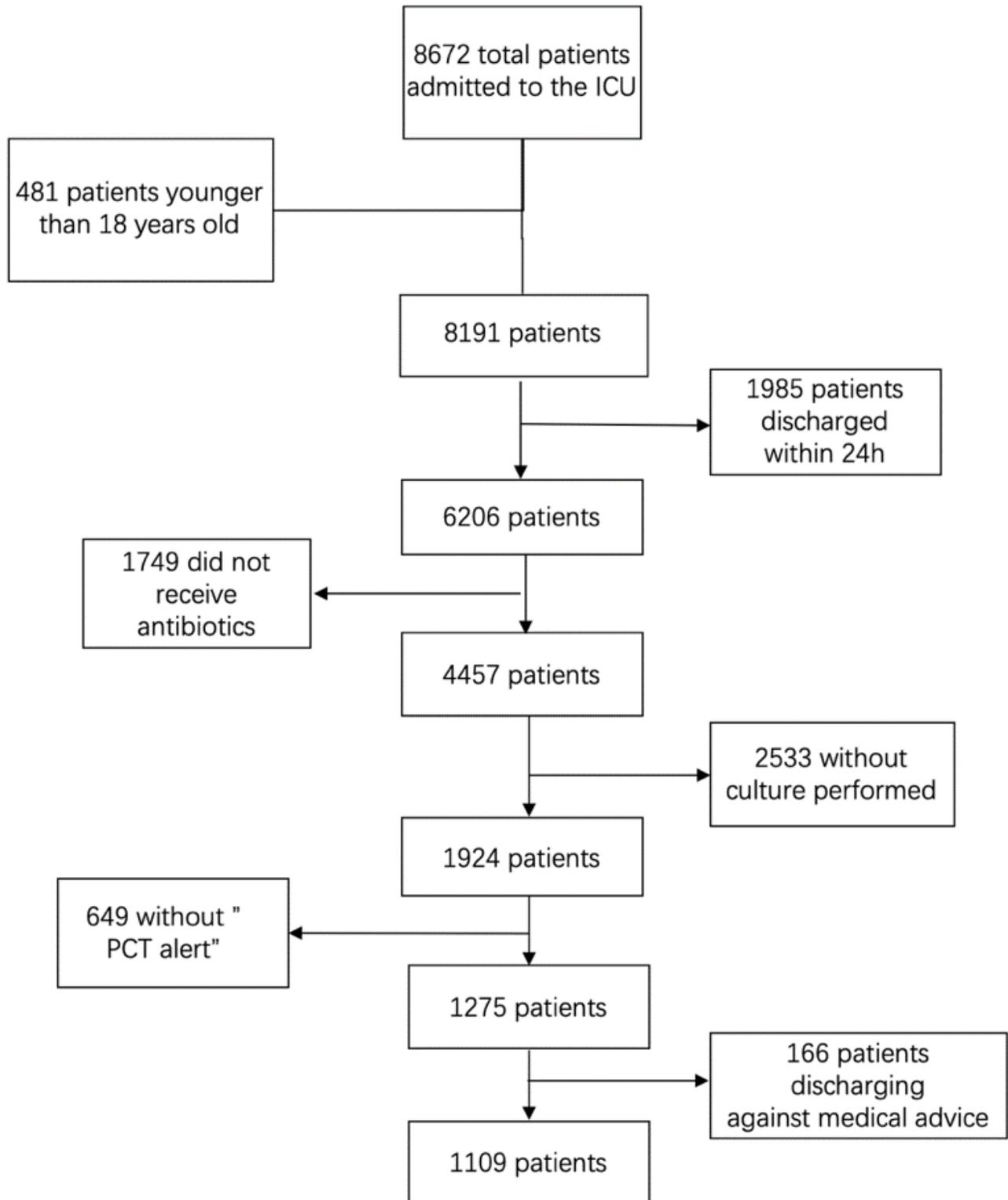


Figure 4

The flow diagram of patient enrollment

Supplementary Files

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- SUPPLEMENT.xls
- SUPPLEMENT.xls