Journal of Infection (2015) xx, 1–9

www.elsevierhealth.com/journals/jinf

Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis

Alejandro H. Rodríguez [a,*], Francesc X. Avilés-Jurado [b], Emili Díaz [c], Philipp Schuetz [d], Sandra I. Trefler [a], Jordi Solé-Violán [e], Lourdes Cordero [f], Loreto Vidaur [g], Ángel Estella [h], Juan C. Pozo Laderas [i], Lorenzo Socias [j], Juan C. Vergara [k], Rafael Zaragoza [l], Juan Bonastre [m], José E. Guerrero [n], Borja Suberviola [o], Catia. Cilloniz [p], Marcos I. Restrepo [q], Ignacio Martín-Loeches [r], on behalf of the SEMICYUC/GETGAG Working Group [1]

[a] *Critical Care Department, Hospital Universitari de Tarragona Joan XXIII, IISPV/URV/CIBERes, Tarragona, Spain*
[b] *Otorhinolaryngology Head-Neck Surgery Department, Hospital Universitari de Tarragona Joan XXIII, IISPV/URV, Tarragona, Catalonia, Spain*
[c] *Critical Care Department, ParcTaulí Hospital/CIBERes, Sabadell, Spain*
[d] *Internal Medicine Department, Kantonsspital Aarau, Switzerland*
[e] *Critical Care Department, Hospital Dr. Negrín, Las Palmas de Gran Canaria, Spain*
[f] *Critical Care Department, CHUAC, A Coruña, Spain*
[g] *Critical Care Department, Hospital de Donostia, San Sebastian, Spain*
[h] *Critical Care Department, Hospital SAS, Jerez de la Frontera, Spain*
[i] *Critical Care Department, Hospital Reina Sofía, Córdoba, Spain*
[j] *Critical Care Department, Hospital Son Llatzer, Palma de Mallorca, Spain*
[k] *Critical Care Department, Hospital de Cruces, Vizcaya, Spain*
[l] *Critical Care Department, Hospital Dr. Peset, Valencia, Spain*
[m] *Critical Care Department, Hospital La Fe, Valencia, Spain*
[n] *Critical Care Department, Hospital Gregorio Marañón, Madrid, Spain*

* Corresponding author. Critical Care Department, Hospital Universitario de Tarragona Joan XXIII, Mallafré Guasch 4 (43007), Tarragona – Spain. Tel.: +34 977295818; fax: +34 977214768.
E-mail addresses: ahr1161@yahoo.es (A.H. Rodríguez), fxavilesj@gmail.com (F.X. Avilés-Jurado), emilio.diaz.santos@gmail.com (E. Díaz), schuetzph@gmail.com (P. Schuetz), sitrefler@yahoo.es (S.I. Trefler), jsolvio@gobiernodecanarias.org (J. Solé-Violán), lcorlor@gmail.com (L. Cordero), loreto.vidaurtello@osakidetza.net (L. Vidaur), litoestella@hotmail.com (Á. Estella), juanc.pozo.sspa@juntadeandalucia.es (J.C. Pozo Laderas), lsocias3@gmail.com (L. Socias), juancarlos.vergaraserrano@osakidetza.net (J.C. Vergara), zaragozar@ono.com (R. Zaragoza), bonastre_jua@gva.es (J. Bonastre), jeguerrerosanz@gmail.com (J.E. Guerrero), borja.suberviola@gmail.com (B. Suberviola), catiacilloniz@yahoo.com (Catia. Cilloniz), restrepom@uthscsa.edu (M.I. Restrepo), drmartinloeches@gmail.com (I. Martín-Loeches).
[1] SEMICYUC/GETGAG Working Group investigators listed in supplemental digital content (Appendix 1).

http://dx.doi.org/10.1016/j.jinf.2015.11.007

[o] Critical Care Department, Hospital Universitario de Santander, Spain
[p] Critical Care Department, Hospital Clinic / CIBERES, Barcelona, Spain
[q] Division of Pulmonary Diseases and Critical Care Medicine, University of Texas Health Science Center at San Antonio San Antonio, TX, USA
[r] Multidisciplinary Intensive Care Research Organization (MICRO), Department of Anaesthesia and Critical Care, St James's University Hospital, Trinity Centre for Health Sciences, Dublin, Ireland

Accepted 28 November 2015
Available online ■ ■ ■

KEYWORDS
Procalcitonin;
Influenza A(H1N1)pmd;
Community-acquired pneumonia;
Respiratory coinfection;
CHAID analysis;
Prognosis;
Septic shock

Summary *Objectives:* To define which variables upon ICU admission could be related to the presence of coinfection using CHAID (Chi-squared Automatic Interaction Detection) analysis.
Methods: A secondary analysis from a prospective, multicentre, observational study (2009−2014) in ICU patients with confirmed A(H1N1)pdm09 infection. We assessed the potential of biomarkers and clinical variables upon admission to the ICU for coinfection diagnosis using CHAID analysis. Performance of cut-off points obtained was determined on the basis of the binominal distributions of the true (+) and true (−) results.
Results: Of the 972 patients included, 196 (20.3%) had coinfection. Procalcitonin (PCT; ng/mL 2.4 vs. 0.5, $p < 0.001$), but not C-reactive protein (CRP; mg/dL 25 vs. 38.5; $p = 0.62$) was higher in patients with coinfection. In CHAID analyses, PCT was the most important variable for coinfection. PCT <0.29 ng/mL showed high sensitivity (Se = 88.2%), low Sp (33.2%) and high negative predictive value (NPV = 91.9%). The absence of shock improved classification capacity. Thus, for PCT <0.29 ng/mL, the Se was 84%, the Sp 43% and an NPV of 94% with a post-test probability of coinfection of only 6%.
Conclusion: PCT has a high negative predictive value (94%) and lower PCT levels seems to be a good tool for excluding coinfection, particularly for patients without shock.

Introduction

Community-acquired respiratory coinfection (CARC) in patients with viral pneumonia caused by influenza A(H1N1) pdm09 has been recognised as a major cause of influenza-related death.[1,2] Since 2009, more than 2000 patients have been admitted to intensive care units (ICUs) for cases of severe influenza in Spain.[3–6] To reduce mortality and morbidity in this vulnerable patient population, early administration of antibiotic (AB) treatment is recommended in patients suspected of having CARC. Yet, different studies have found that both clinical signs and symptoms, and commonly used laboratory markers, are unreliable for assessing the risk of CARC in this particular subset of patients admitted to the ICU.[7,8] As a result, in clinical practice, currently most patients receive antibiotics (AB); according to the Spanish Society of Intensive Care Medicine (SEMICYUC) database, 100% of critically ill patients with influenza were treated with empirical AB upon admission to the ICU.[3–6] However, only in 20% of the cases was CARC eventually confirmed.[6] More accurate, prompt diagnostic tools to rule out CARC could potentially limit AB overuse and subsequently reduce unnecessarily high costs, potential side-effects and the development of multi-drug resistance infections.

Procalcitonin (PCT) is a biomarker reported in the event of bacterial infection and adequately correlates with severity and outcome of lower respiratory tract infections (LRTI). In addition, AB guidelines, based on PCT levels, have been seen to significantly reduce AB administration in patients with LRTI in both emergency departments and ICUs.[9–11] However, there is a lack of large-scale clinical data demonstrating the utility of PCT as an accurate biomarker for guiding AB use in patients with severe influenza pneumonia with CARC. Four minor studies have suggested that the use of PCT cut-off ranges in patients infected with influenza A(H1N1)pdm09 may estimate the probability of developing CARC.[12–15] Nevertheless, these studies are limited in terms of small sample size (between 16 and 100 patients) and different criteria for patient selection, cut-offs, and outcome. The aim of this study was to evaluate the potential role of PCT in ruling out the presence of CARC in a large, well-defined cohort of influenza A(H1N1) pdm09-infected patients. Our hypothesis was that the PCT algorithms recommended for AB administration[9] could be different from those observed in patients with primary viral pneumonia caused by influenza A(H1N1)pdm09. The main objective of our study was, therefore, to define which variables upon admission to the ICU could be related to the presence of CARC using CHAID (Chi-squared Automatic Interaction Detection) decision-tree analysis[16–18] in order to maximise the probability of a correct diagnosis.[16–19]

Material and methods

Study design and patient population

This is a secondary analysis from a prospective, observational cohort study conducted across 148 ICUs in Spain

Please cite this article in press as: Rodríguez AH, et al., Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis, J Infect (2015), http://dx.doi.org/10.1016/j.jinf.2015.11.007

between June 2009 and April 2014. Data were obtained from a voluntary register created by the SEMICYUC.[3–6]

The study was approved by the Joan XXIII University Hospital Ethics Committee (IRB NEUMAGRIP/11809). Patients remained anonymous. The requirement for informed consent was waived due to the observational nature of the study and the fact that this activity was considered an emergency public health response, as reported elsewhere.[3–6] Three time periods were considered: 1) 2009 pandemic infection period (epidemiological weeks [EW] 23–52); 2) the post-pandemic period (EW 50–52 of 2010 and 1–9 of 2011); and 3) 2014 winter season period (EW 40–52 of 2013 and 1–14 of 2014). During these periods, all patients admitted to the ICU with influenza symptoms were systematically tested to confirm influenza A(H1N1) pdm09. Only patients with PCT measurements upon admission to the ICU were included in this analysis. Children under 15 years of age were not enrolled in the register Influenza A(H1N1)pdm09 virus infection was confirmed by real-time reverse-transcription-polymerase chain reaction (rt-PCR) in all patients. The rt-PCR methods and further details are described elsewhere.[3–6]

Patient flow and outcome assessment

ICU admission criteria and treatment decisions for all patients, including the need for intubation and type of antibiotic or antiviral therapy administered, were made at the discretion of the attending physician and not standardised. Septic shock and multiple organ dysfunction score (MODS) were defined following the international criteria.[20] Organ failure was assessed using the sequential organ failure assessment (SOFA) scoring system.[21] Only patients with microbiological confirmation of CARC were included in this analysis.

Definitions

Primary viral pneumonia caused by influenza A(H1N1) pdm09 was defined as patients presenting with acute respiratory distress, unequivocal alveolar opacities involving two or more lobes, and negative respiratory and blood bacterial cultures during the acute phase of influenza virus infection.[3–6] The presence of CARC was defined as a bacterial respiratory microbiologically-confirmed infection diagnosed within the first two days of hospitalisation. For CARC diagnosis an acute pulmonary infiltrate evident on chest radiographs and consistent with pneumonia and confirmatory findings on clinical examination were required.[6] Infections occurring later were considered nosocomial. Hospital-acquired pneumonia (HAP) was defined based on current guidelines[22] and excluded for this study.

An organism was considered to be the definitive causative pathogen only if it could be isolated from blood or pleural fluid.[3–6] Other microorganisms isolated from quantitative endotracheal aspirate (ETA), bronchoalveolar lavage (BAL) or protected specimen brush (PSB) were considered "probable" pathogens. Serology tests revealing a fourfold increase in antibody levels were also considered as definitive diagnoses. A positive urinary antigen test for *Streptococcus pneumoniae* or *Legionella* was considered probable causative pathogen.

Diagnosis of invasive pulmonary aspergillosis was based on the demonstration of microorganisms in histopathology samples. Patients with a halo or an air-crescent sign on their lung computed tomography (CT) scan were considered to have probable pulmonary aspergillosis. Colonization was defined as the isolation of *Aspergillus* spp. in lower respiratory samples in patients not meeting the European Organization for Research and Treatment of Cancer[23] or Bulpa's criteria.[24] *Legionella* and pneumococcal urinary antigen were determined in all patients upon admission to the ICU. In patients receiving mechanical ventilation, a respiratory specimen was obtained upon admission to the ICU according to local protocols. Obese patients were defined as those whose body mass index (BMI) exceeds 30 kg/m^2.[3–6] Acute kidney injury (AKI) definition and staging were established according to the current Acute Kidney Injury Network classification.[25] Shock was defined as the need for a vasopressor for more than 4 h after fluid replacement at the time of admission to the ICU.[20]

Laboratory testing

Procalcitonin is not part of the standard protocol for the diagnosis of community-acquired pneumonia Spain. The decision to measure serum PCT upon admission to the ICU was left to the discretion of the attending physician and was not standardised. PCT was measured using B·R·A·H·M·S PCT automated immunoassays. The analytical sensitivity of all assays was $<0{\cdot}05$ μg/L. All techniques were based on a one-step immunoassay sandwich method determined either by chemiluminescence or fluorescence.

Statistical analysis

Discrete variables are expressed as counts (percentage) and continuous variables, as means and standard deviation (SD), or medians with the 25th to 75th interquartile range (IQR). For patients' demographic and clinical characteristics, differences between groups were assessed using the chi-squared test or Fisher's exact test for categorical variables and, Student's *t*-test or the Mann–Whitney U test for continuous and ordinal variables when appropriate. Receiver operating characteristic (ROC) curves were built to establish the accuracy of the PCT and CRP (C-reactive protein) values in the identification of CARC. Differences between by the area under the receiver operating characteristic curve (ROC-AUC) were obtained by Hanley and McNeil analysis. The sensitivity (S), specificity (Sp), positive and negative predictive values (PPV, NPV) and positive or negative likelihood ratio (LR+, LR−) were calculated considering the PCT cut-off levels used in the previously reported algorithm.[26] Four cut-off points were analysed: 1) PCT $<0{\cdot}25$ ng/mL; 2) PCT $<0{\cdot}50$ ng/mL; 3) PCT $<0{\cdot}75$ ng/mL; and 4) PCT $>1{\cdot}0$ ng/mL on the basis of the binominal distributions of the true positive and true negative results. Subsequently, we convert pre-test probability to "pre-test Odds" (Pre-test Prob/[1−Pre-test Prob]), then multiply the Pre-test Odds by the LR for the finding to derive the "post-test Odds" and then convert Post-test Odds back to "Post-test probability" using (Post-test Odds/[1+Post-test Odds]).

Please cite this article in press as: Rodríguez AH, et al., Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis, J Infect (2015), http://dx.doi.org/10.1016/j.jinf.2015.11.007

CHAID classification tree

A CHAID tree is a graphic representation of a series of decision rules. Beginning with a root node that includes all cases, the tree branches are divided into different child nodes that contain a subgroup of cases. The criterion for branching (or partitioning) is selected after examining all possible values of all available predictive variables. In the terminal nodes, a grouping of cases is obtained, such that the cases are as homogeneous as possible with respect to the value of the dependent variable.[16–18] CHAID decision trees are nonparametric procedures that make no assumptions of the underlying data. This algorithm determines how continuous and/or categorical independent variables best combine to predict a binary outcome based on "if-then" logic by portioning each independent variable into mutually exclusive subsets based on data homogeneity (additional information about the CHAID algorithm in the supplemental digital content). For this study, the response variable is the presence or absence of CARC. S, Sp, PPV, NPV and LR+ or LR− were calculated considering the PCT CHAID cut-off obtained on the basis of the binominal distributions of the true positives and true negatives results. Subsequently, we calculated pre-test probability, pre-test Odds post-test Odds, post-test Odds, and post-test probability. Statistical analysis with the CHAID method was carried out through the CHAID node included in the statistical program SPSS 20.0 for Windows (IBM).

Results

Study population characteristics

Two thousand one hundred thirty-two patients with rt-PCR-confirmed influenza A(H1N1)pdm09 virus infection were admitted to the 148 ICUs in the three periods considered. Nine hundred and seventy-two of them (45.6%) had PCT levels measured upon admission to the ICU and were the population of analysis. Of these patients, 581 (59.8%) were men, and the median was 51 years of age. The mean APACHE II and SOFA scores were 16.5 and 6.4 points,

Table 1 Comparison of demographic and clinical characteristics among patients with proven influenza A(H1N1)pdm09 infection with or without community-acquired respiratory coinfection (CARC).

Variables	Overall (n = 972)	A(H1N1)pdm09 (n = 776)	CARC (n = 196)	p-value
Demographics				
Age, mean (SD)	51.2 (14.8)	50.8 (14.9)	52.7 (14.0)	0.12
Median (IQR)	52.0 (40–61)	51.0 (40–61)	53 (42–62)	
Male, n (%)	581 (59.8)	451 (58.1)	130 (66.3)	0.03
Severity of illness				
APACHE II score, median (IQR)	16.5 (11–21)	15.0 (10–20)	18.0 (13–22)	<0.001
SOFA score, median (IQR)	6.4 (4–9)	6.0 (3–8)	7.0 (4–10)	<0.001
Comorbidities, n (%)	712 (73.6)	569 (73.3)	143 (73.0)	0.86
Asthma	95 (9.8)	78 (10.1)	17 (8.7)	0.55
Chronic obstructive pulmonary disease	183 (18.9)	142 (1.3)	41 (20.9)	0.41
Obesity	325 (33.5)	273 (3.2)	52 (26.5)	0.02
Diabetes mellitus	170 (17.5)	135 (17.4)	35 (17.9)	0.89
Chronic renal failure	86 (8.8)	66 (8.5)	20 (10.2)	0.46
Cardiac disease	106 (10.9)	90 (11.6)	16 (8.2)	0.16
Pregnancy	30 (3.1)	28 (3.6)	2 (1.0)	0.61
Haematological disease	74 (7.6)	56 (7.2)	18 (9.2)	0.35
HIV infection	20 (2.1)	13 (1.7)	7 (3.6)	0.09
Autoimmune disease	39 (4.0)	31 (4.0)	8 (4.1)	0.19
Complications, n (%)				
Shock	555 (57.4)	416 (53.6)	139 (70.9)	<0.001
Mechanical ventilation	787 (81.1)	624 (80.4)	163 (83.2)	0.41
Acute renal injury	251 (25.8)	175 (22.6)	76 (38.8)	<0.001
Clinical and biomarkers				
PCT ng/ml, median (IQR)	0.7 (0.2–2.9)	0.5 (0.2–2.0)	2.4 (0.6–11.7)	<0.001
CRP mg/dl, median (IQR)	27 (14–90.2)	25 (13.2–88.2)	38.5 (19.5–154)	0.62
Vaccinated, n (%)	58 (8.2)	42 (5.4)	16 (8.2)	0.18
Quadrants infiltrated in chest X-ray at ICU admission, mean (SD)	2.4 (1.3)	2.5 (1.3)	2.4 (1.2)	0.20
Time between diagnosis and ICU admission, days, mean (SD)	2.4 (3.5)	2.3 (3.4)	2.6 (3.8)	0.53
Antibiotic treatment first day in ICU, n (%)	972 (100)	776 (100)	196 (100)	1.0
ICU Mortality, n (%)	242 (24.9)	179 (23.1)	63 (32.1)	<0.01

Abbreviations: CARC: community-acquired respiratory coinfection; SD: standard deviation; IQR: interquartile range; ICU: intensive care unit; PCT: procalcitonin; CRP: C-reactive protein.

Please cite this article in press as: Rodríguez AH, et al., Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis, J Infect (2015), http://dx.doi.org/10.1016/j.jinf.2015.11.007

respectively. Patients had a high comorbidity burden (see detailed baseline characteristics in Table 1).

In comparison with the study population, patients excluded from the analysis (n = 1160) had less severity of illness (APACHE II score = 14.5 [7.1] $p < 0.001$; SOFA score = 5.59 [3.7] $p < 0.001$), were younger (48.0 [15.6] $p < 0.001$) and had a lower ICU mortality rate (19.6%; $p < 0.001$).

Primary viral pneumonia caused by influenza A(H1N1) pdm09 without CARC was found in 776 patients (79.8%), and 196 patients (20.3%) had CARC with another isolated pathogen upon admission to the ICU. The etiological diagnosis of CARC was based on quantitative ETA (82.5%), urinary antigen (13%), blood cultures (3.0%), and serology (1.5%); *S. pneumoniae* was the most prevalent isolated pathogen (99 patients; 50.5%), followed by *Pseudomonas aeruginosa* (17 patients; 8.7%), methicillin-sensitive *Staphylococcus aureus* (MSSA) (16 patients; 8.2%), and *Streptococcus pyogenes* (10 patients; 5.1%). Table 2 details the prevalence of isolated pathogens in patients with CARC. Four patients (2%) had CARC with more than one microorganism.

Compared with patients without CARC, patients with CARC had higher APACHE II and SOFA scores upon admission. No differences in comorbidities were observed except for obesity, which was more common in patients without CARC. Patients with CARC required more vasopressor and developed of acute renal failure more frequently than those without it. Empirical AB therapy was administered to all patients but CARC was associated with increased ICU mortality. Demographic data and clinical characteristics of patients with influenza A(H1N1)pdm09 infection, with and without CARC, are presented in Table 1.

PCT and CRP diagnostic accuracy

Median values of PCT (2.4 ng/mL vs. 0.5 ng/mL), but not of CRP (25 mg/dL vs. 38.5 mg/dL), were significantly higher in CARC patients. Similarly, median PCT levels (0.5 [0.2—2.5] ng/mL vs. 1.1 [0.4—4.3] ng/mL; $p < 0.001$), but not CRP levels (26.3 [14.1—92.9] mg/dL vs. 27.0 [14.0—90.0] mg/dL; $p = 0{\cdot}71$), were significantly higher in non-survivors than in survivors. Fig. 1 shows the ROC curve of PCT and CPR. The AUC was significantly higher for PCT (AUC 0.716 [95% CI 0.67—0.75]) than for CRP (AUC 0.590 [95% CI 0.54—63.0]; $Z = 4.25$; $p < 0.001$). The results were similar when immunocompromised patients were excluded (AUC 0.74 [95% CI 0.67—0.78] vs. 0.59 [95% CI 0.54—0.63], $p < 0.001$). Table 3 shows the discriminatory performance of PCT at different predefined cut-off points for detection of CARC. In patients with PCT <0.25 ng/mL, the NPV was 92% for excluding CARC. Interestingly, even considering the higher cut-off point (PCT >1 ng/mL), NPV remained high (88.5%) with a LR− of 0.51.

CHAID classification tree

The analysis was conducted using CHAID decision tree techniques for obtaining the best cut-off points for PCT. We included CARC as a dependent variable and clinical variables upon admission to the ICU (age, sex, comorbidities, SOFA score, serum PCT, serum CRP, presence of shock, number of quadrants with infiltrates on chest X-ray, AKI, and mechanical ventilation) as independent variables in the model. Maximum tree depth was three, with minimum cases in parent node of 100. A decision tree was generated (Fig. 2) with seven terminal nodes and two levels deep This analysis showed that PCT was the most decisive variable at the time of classification and four levels of risk for CARC were generated: 1) very-low-risk (PCT <0.29 ng/mL); 2) low risk (PCT 0.29—1.10 ng/mL); 3) intermediate risk (>1.10—4.42 ng/mL); and 4) high risk (PCT >4.42 ng/mL).

According to these ranges, we established three cut-off points to calculate the discriminatory performance of PCT.

Table 2 Pathogens isolated in patients with A(H1N1)pdm09 virus infection with community-acquired respiratory coinfection (CARC).

Pathogens	N (%)	Definitive	Probable
Streptococcus pneumoniae	99 (50.5)	4	95
Pseudomonas aeruginosa	17 (8.7)	—	17
MSSA	16 (8.2)	—	16
Streptococcus pyogenes	10 (5.1)	2	8
Aspergillus sp.	9 (4.6)	—	9
Acinetobacter baumannii	7 (3.6)	—	7
Escherichia coli	5 (2.6)	—	5
Klebsiella pneumoniae	4 (2.0)	—	4
Haemophilus influenza	4 (2.0)	—	4
Staphylococcus hominis	4 (2.0)	—	4
Chlamydia sp.	3 (1.5)	3	—
Moraxella catarrhalis	2 (1.0)	—	2
Enterococcus faecium	2 (1.0)	—	2
Serratia sp.	2 (1.0)	—	2
MRSA	2 (1.0)	—	2
Mycobacterium tuberculosis	2 (1.0)	2	—
Others	5 (2.6)	—	5

MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

Please cite this article in press as: Rodríguez AH, et al., Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis, J Infect (2015), http://dx.doi.org/10.1016/j.jinf.2015.11.007

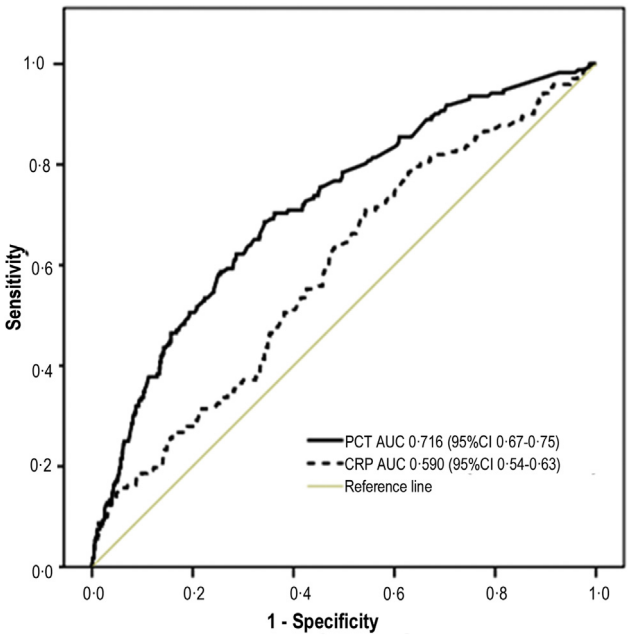

Figure 1 Area under the receiver operating characteristic (AUC) curves of procalcitonin (PCT) and C-reactive protein (CRP) for differentiation of patients with community-acquired respiratory coinfection (CARC) from primary viral infection.

Only PCT >4.42 ng/mL showed high specificity for CARC (85.4%), but the LR+ was low (2.8) with pre-test Odds of 0.25 and both post-test Odds of 0.73 and a post-test probability of 42%. Conversely, a cut-off of PCT <0.29 ng/mL was associated with an S of 88.2%, an Sp of 33.2%, and a PPV of 25% but with a high NPV (91.8%). For a probability pre-test of 20%, the pre-test Odds were 0.25 and post-test Odds of −0.09 with an 8% post-test probability of CARC.

In the very-low-risk level, the absence of shock improved classification capacity. Thus, for a cut-off of PCT <0.29 ng/mL, when patients without shock were considered (n = 412), the S was 84%, the Sp 43% and the pre-test probability of CARC, 14%. This cut-off had a PPV of 19% and a NPV of 94% with a LR+ of 1.49 and LR− of 0.36. In this condition, pre-test Odds were 0.16 and post-test Odds 0.06, with only a 6% post-test probability of CARC. The post-test probability was similar when we considered a cut-off of PCT ≤1.10 ng/mL in patients without shock.

Discussion

The main findings of our study conducted in patients with confirmed A(H1N1)pdm09 virus infection were threefold. First, the CHAID model illustrates multilevel interactions among risk factors to identify stepwise pathways to detect CARC. The proposed CHAID model distributed serum PCT into the first level of partition above other variables as the strongest variable associated with CARC. Second, low serum levels of PCT in patients without shock were an accurate predictor for excluding the presence of CARC (<6%) and finally, PCT was more accurate than CRP, which is still the standard biomarker routinely used in many ICUs to define the presence of CARC.

The CHAID model illustrates multilevel interactions among risk factors to identify stepwise pathways for detecting CARC. CHAID models seem to be a promising tool to detect CARC and assist in clinical decision-making that, to our best of our knowledge, has not been proposed before.

Previous studies focussing on the ability of PCT or CRP to discriminate between A(H1N1)pdm09 viral and bacterial coinfection have significant shortcomings, limiting their applicability to the scenarios currently faced by intensivists. Several studies[11–14] and recent meta-analysis[15] suggest that PCT is more accurate than CRP for distinguishing between viral and bacterial infection. However, performance varies depending on microbial factors, severity of illness and the cut-off points used. Interestingly, in our study, PCT levels were significantly increased in patients with CARC compared to those with primary viral pneumonia, but CRP was not. The overall discriminatory performance of PCT for identifying CARC was moderate, with an AUC of 0.71, but better discrimination than CRP for detecting bacterial infection, similar to that reported in other studies.[27,28]

Antimicrobial overuse in ICU patients with viral pneumonia caused by influenza A(H1N1)pdm09 could be substantially reduced if AB treatment were restricted to those patients with a true CARC. The application to our population of the classically reported algorithm cut-off point (>0.5 ng/mL)[9] yields modest results with S of 78%, low Sp

Table 3 Discriminatory performance of procalcitonin (PCT) cut-off point for detection of community-acquired respiratory coinfection (CARC) in patients with influenza A(H1N1)pdm09 infection.

Variable	Cut-off point	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR (+)	LR (−)
PCT algorithms[9]	<0.25 ng/mL	89.7 (84.9–93.1)	31.3 (28.3–34.5)	24.8 (21.9–28.0)	92.0 (88.6–94.8)	1.30	0.32
	<0.50 ng/mL	78.0 (72.0–8.30)	46.5 (43.2–49.8)	26.9 (23.6–30.6)	89.3 (86.0–91.8)	1.45	0.47
	<0.75 ng/mL	70.5 (64.1–76.2)	58.6 (55.3–61.8)	30.1 (26.3–43.3)	88.7 (85.8–91.0)	1.70	0.50
	>1.0 ng/mL	66.8 (60.3–72.8)	64.9 (61.7–68.1)	32.5 (28.3–37.0)	88.5 (85.8–90.8)	1.90	0.51
PCT CHAID	<0.29 ng/mL	88·2 (83·0–92·0)	33.2 (30.0–36.6)	25.0 (21.9–28.4)	91.8 (88.0–94.5)	1.32	0.35
	<1.10 ng/mL	65·8 (58·9–72·0)	65.8 (62.4–691)	32.7 (28.3–37.5)	88.4 (85.5–90.7)	1.92	0.51
	>4.42 ng/mL	41·8 (35·1–48·8)	85.4 (82.7–87.7)	42.0 (35.3–49.0)	85.3 (82.6–87.6)	2.8	0.68

CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; LR(+): positive likelihood ratio; LR(−): negative likelihood ratio.

Please cite this article in press as: Rodríguez AH, et al., Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis, J Infect (2015), http://dx.doi.org/10.1016/j.jinf.2015.11.007

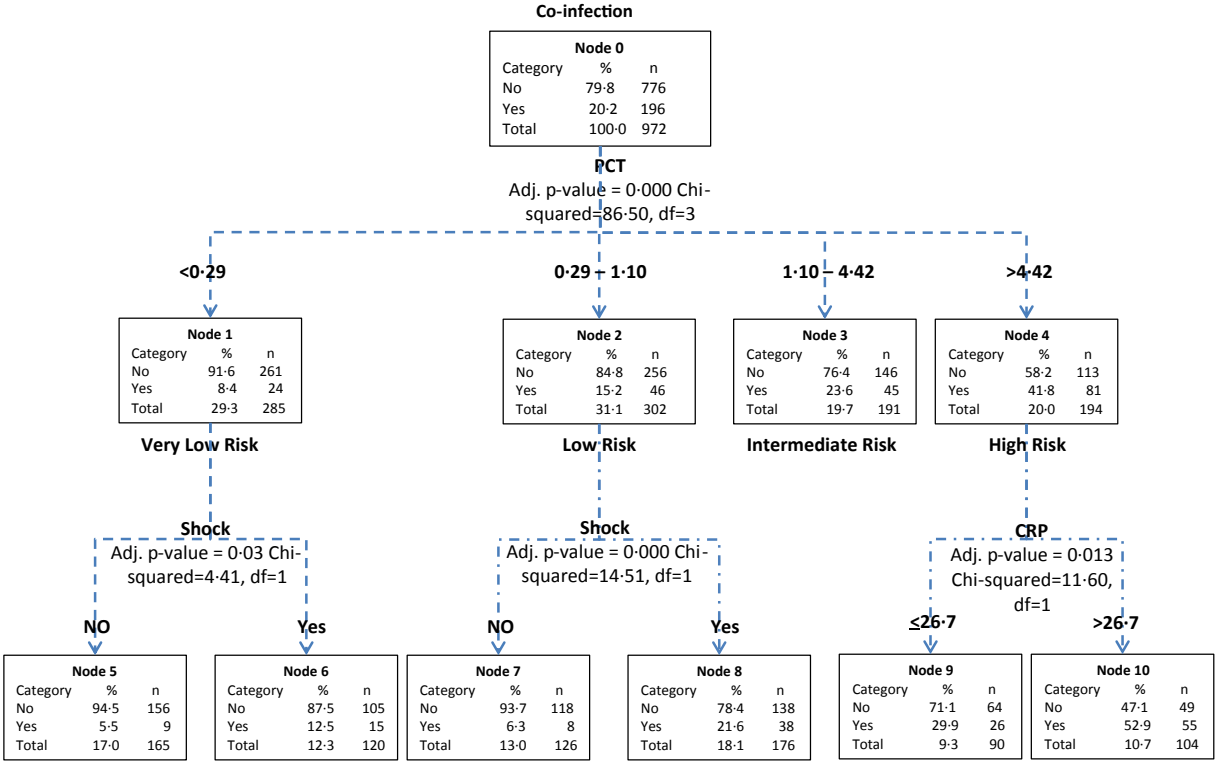

Figure 2 Tree created by the CHAID model (Chi-squared Automatic Interaction Detection) for community-acquired respiratory coinfection (CARC). PCT: procalcitonin; CRP: C-reactive protein.

(46%), and very low PPV (27%), but a high NPV (89%). When the cut-off point was raised to >1.0 ng/mL, Sp improved somewhat (65%), but PPV remained low (32%). Even considering this relatively high cut-off point, the NPV remains high (88%) with a low LR+ of 1.90.

A novel approach in searching for tools that could improve the predictive capacity is to conduct a CHAID decision-tree analysis. The main conceptual difference is that, in this model, the interaction of the different variables was analysed. Thus, the hazard ratio applies to the whole population rather than to a single subgroup. This methodology has the ability to improve the predictive capacity achieved by multivariate models in specific situations. In particular, the CHAID method allows the detection of individual cases with unique behaviour within the study population as a whole that would have gone unnoticed using conventional methods.[16–19]

After applying this method, our study showed that the most decisive variable at the time of classification was the level of PCT, with a discriminative value greater than other clinical variables such as the presence of shock, or the level of CRP. According to the PCT CHAID-generated cut-off point, a PCT test, even above 4.42 ng/mL, exhibited a suboptimal rule-in value for confirming CARC. The overall LR+ (2.8) for the PCT test was not sufficiently high to be used as a reliable rule-in tool for the diagnosis of CARC. For example, in our population with a 20% prevalence (pre-test probability) of CARC, a LR+ of 2.8 translates into a positive predictive value (post-test probability) of 42%. In other words, approximately 2 out of 5 patients with positive PCT test results would have either clinically- or microbiologically-confirmed CARC.

Conversely, the serum levels of PCT showed acceptable ability to rule out the presence of CARC in patients with H1N1pdm09 virus infection. Applying a cut-off point of <0.29 ng/mL to the same population with a 20% prevalence of CARC, a LR− of 0.35 translates into a NPV of 92% with an 8% post-test probability of CARC. This probability decreased to 6% in patients without shock even when the PCT cut-off point was increased to 1.10 ng/mL. In other words, only 1 out of every 20 patients with a negative PCT result would have either clinically- or microbiologically-confirmed CARC.

Even if another study is required to validate of our findings before a specific recommendation can be made, our results suggest that in the absence of shock, serum PCT values ≤1.10 ng/mL are associated with a low probability of the presence of CARC in patients without shock. We acknowledge that some physicians might feel uncomfortable if an ICU patient who had a PCT ≤0.29 ng/mL (and therefore still with a 6% chance of having CARC) were left untreated. In approaching this clinical situation, one might decide to treat empirically since a negative test does not rule out disease. Alternatively, one could perform a new determination of serum PCT in the next 24 h and closely observe the patient before starting antibiotic treatment. Modifying patient-based antibiotic treatment is an ever-changing responsibility of the antimicrobial stewardship programme whose purpose is to limit inadequate antimicrobial use, bacterial resistance, unnecessary cost, and possible harm to patients. As a diagnostic tool, serum PCT levels might assist physicians in stratifying patients according to the risk of CARC.

There are some limitations that should be taken into account. First, serial measurements of the serum PCT

Please cite this article in press as: Rodríguez AH, et al., Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis, J Infect (2015), http://dx.doi.org/10.1016/j.jinf.2015.11.007

values were not performed. Although serial measurements have been previously proposed, and could potentially improve discriminative values, our results showed that the initial value of PCT is useful to guide the decision regarding the need to start antibiotic treatment upon admission to the ICU. Second, there is currently no gold standard for the diagnosis of CARC. The incidence of CARC in our study is consistent with what has been previously reported.[6,8] We did not collect information on AB administration prior to admission of the ICU. The sensitivity of respiratory cultures after starting AB might be very low, and we cannot rule out that a portion of the respiratory cultures may be false negative. However, all patients included had microbiological confirmation of CARC. On the other hand, it is true that negative rt-PCR for influenza test does not exclude viral pneumonia in 100% of cases, but the published overall sensitivity of rt-PCR for viral diagnosis is very high (>98%), with a high negative predictive value (99.8%).[29] Conversely, a false negative rt-PCR result may occur if inadequate numbers of organisms are present in the specimen due to improper collection, transport or handling or if an excess of DNA/RNA template is present in the reaction. For the purpose of our study, in order to minimize biased selection, these patients were excluded from the study. Third, the measurement of PCT was made at the discretion of the attending physician, and patients in whom PCT was determined were more severely ill than those in which this marker was not obtained However, this is the "actual and current" clinical picture in daily practice, and could reflect a greater difficulty in the diagnosis of CARC in the most severe patients, in which situation biomarker levels could play a more important role. We acknowledge the urgent need for conducting subsequent intervention studies where antibiotic therapy is guided by the use of PCT. Further large randomized studies are needed to clarify the impact of CHAID algorithms in clinical practice in patients with viral pneumonia.

Fourth, although the CHAID method has great advantages, an information overload could occur due to a large quantity of terminal nodes but few patients in each node. In this study, we imposed a very strict model to implement a p value <0.05 and at least restricted to 100 patients per node, and the resulting final tree can be easily interpreted and is clinically applicable with only seven terminal nodes. Our results cannot be generalised to other clinical scenarios such as the emergency department and other viral strains causing pneumonia. In these situations, the inflammatory response and biomarkers may differ depending on clinical severity and the underlying viral pathogen.

Conclusion

In patients admitted to the ICU with confirmed influenza A(H1N1)pdm09 infection and without shock, low serum levels of PCT might be a good tool for ruling out the presence of CARC. However, while PCT can assist physicians in developing patient-specific therapeutic plans, such as antibiotic prescription, it is important to highlight that biomarkers are tools that should never replace physician decision-making.

Conflicts of interest and source of funding

Dr A. Rodriguez has participated as a speaker at scientific meetings or courses organised and financed by various pharmaceutical companies including Astellas, Pfizer, Novartis, Gilead, Thermo Fisher, bioMèrieux, and Roche. AR is the principal investigator for research grants of Carlos III National Institute of Health.

I. Martin-Loeches has participated in advisory boards organized and financed by Bayer, Clinigen, Pfizer and Johnson & Johnson. IML is the principal investigator for research grants of Carlos III National Institute of Health.

Dr P. Schuetz has received financial support from Thermo Fisher Scientific Biomarkers and bioMérieux to attend meetings and fulfil speaking engagements, and has received research grants from both companies.

All other named authors declare that they have no competing interests.

The study funder (Spanish Society of Critical Care – SEMICYUC) had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (AR) had full access to all the data in the study and final responsibility for the decision to submit for publication.

Contributors

AR, FXAJ, IML, ED, JSV, MR and PS conceived and designed the study. All authors, apart from MR and PS, contributed to acquisition and local preparation of the constituent database.

FXAJ (Master's degree in epidemiology and statistics) has carried out the analysis of the data and the CHAID model.

AR, ST, IML and FXAJ contributed to database creation and standardisation, design of statistical analyses, and data analysis.

AR, FXAJ, IML, JSV, BS, MR, ED, RZ, and PS interpreted the data and wrote the paper.

All authors contributed to critical examination of the paper for important intellectual content and approval of the final manuscript. Each author acts as the guarantor of data from their individual centre. AR acts as overall guarantor for the pooled analysis and the report.

Acknowledgements

This study was endorsed by the SEMICYUC (Spanish Society of Intensive Care Medicine). We thank the GETGAG (Influenza A/H1N1 Working Group from SEMICYUC) investigators for their contributions to the research. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the SEMICYUC.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2015.11.007.

References

1. Simonsen L. The global impact of influenza on morbidity and mortality. *Vaccine* 1999;**17**(Suppl. 1):S3—10.
2. Bhat N, Wright JG, Broder KR, Murray EL, Greenberg ME, Glover MJ. Influenza Special Investigations Team. Influenza-associated deaths among children in the United States, 2003—2004. *N Engl J Med* 2005;**353**(24):2559—67.
3. Rello J, Rodríguez A, Ibañez P, Socias L, Cebrian J, Marques A. H1N1 SEMICYUC Working Group. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care* 2009;**13**:R148.
4. Rodríguez A, Martin-Loeches I, Bonastre J, Olaechea P, Alvarez-Lerma F, Zaragoza R. SEMICYUC-CIBERES-REIPI Working Group. First influenza season after the 2009 pandemic influenza: report of the first 300 ICU admissions in Spain. *Med Intensiva* 2011;**35**:208—16.
5. Martin-Loeches I, Díaz E, Vidaur L, Torres A, Laborda C, Granada R. H1N1 SEMICYUC/REIPI/CIBERES Working Group. Pandemic and post-pandemic influenza A (H1N1) infection in critically ill patients. *Crit Care* 2011;**15**:R286.
6. Martin-Loeches I, Sanchez-Corral A, Diaz E, Granada RM, Zaragoza R, Villavicencio C. H1N1 SEMICYUC Working Group. Community-acquired respiratory co-infection in critically ill patients with pandemic 2009 influenza A(H1N1) virus. *Chest* 2011;**139**:555—62.
7. Cuhna BA, Syed U, Strollo S. Swine influenza (H1N1) pneumo nia in hospitalized adults. Chest film findings. *Heart Lung* 2011;**40**:253—6.
8. Rice TW, Rubinson L, Uyeki TM, Vaughn FL, John BB, Miller RR. NHLBI ARDS Network. Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. *Crit Care Med* 2012;**40**:1487—98.
9. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I. ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009;**302**:1059—66.
10. Schuetz P, Christ-Crain M, Albrich W, Zimmerli W, Mueller B. ProHOSP Study Group. Guidance of antibiotic therapy with procalcitonin in lower respiratory tract infections: insights into the ProHOSP study. *Virulence* 2010;**1**:88—92.
11. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C. PRORATA Trial Group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010;**375**(9713):463—74.
12. Igram PR, Inglis T, Moxon D, Speers D. Procalcitonin and C-reactive protein in severe 2009 H1N1 influenza infection. *Intensive Care Med* 2010;**36**:528—32.
13. Cuquemelle E, Soulis F, Villers D, Roche-Campo F, Ara Somohano C, Fartoukh M. A/H1N1 REVA-SRLF Study Group. Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicentre study. *Intensive Care Med* 2011;**37**:796—800.
14. Piacentini E, Sánchez B, Arauzo V, Calbo E, Cuchi E, Nava JM. Procalcitonin levels are lower in intensive care unit patients with H1N1 influenza A virus pneumonia than in those with community-acquired pneumonia. A pilot study. *J Crit Care* 2011;**26**:201—5.
15. Pfister R, Kochanek M, Leygeber T, Brun-Buisson C, Cuquemelle E, Machado MB. Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review and individual patients data meta-analysis. *Crit Care* 2014;**18**:R44.
16. Zhang J, Goode KM, Rigby A, Balk AH, Cleland JG. Identifying patients at risk of death or hospitalisation due to worsening heart failure using decision tree analysis: evidence from the Trans-European Network-Home-Care Management System (TEN-HMS) study. *Int J Cardiol* 2013;**163**:149—56.
17. Gan XM, Xu YH, Liu L, Huang SQ, Xie DS, Wang XH. Predicting the incidence risk of ischemic stroke in a hospital population of southern China: a classification tree analysis. *J Neurol Sci* 2011;**306**:108—14.
18. Avilés-Jurado FX, León X. Prognostic factors in head and neck squamous cell carcinoma: comparison of CHAID decision trees technology and Cox analysis. *Head Neck* 2013;**35**:877—83.
19. Biggs D, De Ville B, Suen E. A method of choosing multiway partitions for classification and decision trees. *J Appl Stat* 1991;**18**:49—62.
20. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D. SCCM/ESICM/ACCP/ATS/SIS 2001. International sepsis definitions conference. *Crit Care Med* 2003;**31**:1250—6.
21. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H. The SOFA (Sepsis- Related Organ Failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;**22**:707—10.
22. American Thoracic Society. Infectious Disease Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and health care-associated pneumonia. *Am J Respir Crit Care Med* 2005;**171**:388—416.
23. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;**46**:1813—21.
24. Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2007;**30**:782—800.
25. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;**11**:R31.
26. Schuetz P, Amin DN, Greenwald JL. Role of procalcitonin in managing adult patients with respiratory tract infections. *Chest* 2012;**141**:1063—73.
27. Chua A, Lee K. Procalcitonin in severe acute respiratory syndrome (SARS). *J Infect* 2004;**48**:303—6.
28. Fernández Lopez A, Luaces Cubells C, García García JJ, Fernández Pou J. Spanish Society of Pediatric Emergencies. Procalcitonin in pediatric emergency departments for the early diagnosis of invasive bacterial infections in febrile infants: results of a multicenter study and utility of a rapid qualitative test for this marker. *Pediatr Infect Dis J* 2003;**22**:895—903.
29. Cheng PK, Wong KK, Mak GC, Wong AH, Ng AY, Chow SY. Performance of laboratory diagnostics for the detection of influenza A(H1N1)v virus as correlated with the time after symptom onset and viral load. *J Clin Virol* 2010;**47**:182—5.

Please cite this article in press as: Rodríguez AH, et al., Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis, J Infect (2015), http://dx.doi.org/10.1016/j.jinf.2015.11.007