Predictors for Successful Treatment of Infected Necrotizing Pancreatitis With Antibiotics Alone

A Nationwide Prospective Cohort

Hannah S. Pauw, MD,†✉ Hester C. Timmerhuis, MD, PhD,*†*
Lotte Boxhoorn, MD, PhD,‡§ Noor J. Sissingh, MD, PhD,†‖
Rogier P. Voermans, MD, PhD,‡§ Marc G. Besselink, MD, PhD,‡¶
*Elske Sieswerda, MD, PhD,#** Lois A. Daamen, MSc, PhD,††*
Stefan A.W. Bouwense, MD, PhD,‡‡§§ Thomas L. Bollen, MD, PhD,§§‖‖
Jeanin E. van Hooft, MD, PhD, MBA,‖
*Fons F. van den Berg, MD, PhD,‡¶¶## Robert Verdonk, MD, PhD,****
Hjalmar C. van Santvoort, MD, PhD,†††✉ and*
for the Dutch Pancreatitis Study Group

Objective: To identify predictors for successful treatment of patients with infected necrotizing pancreatitis with antibiotics alone.

Background: Infected necrotizing pancreatitis is associated with mortality ranging from 15% to 35%. Recent studies have shown that in some patients, treatment with antibiotics alone is successful, thus avoiding invasive procedures.

Methods: We performed a post hoc analysis of a prospective cohort of 305 patients with suspected or proven infected necrotizing pancreatitis from 22 Dutch hospitals. The primary outcome was successful treatment with antibiotics alone (ie, survival without radiologic, endoscopic, or surgical intervention). All computed tomography images were reviewed to classify the pattern of pancreatic necrosis. A prediction model using clinical and radiologic predictors was created using multivariable logistic regression. A prognostic nomogram was developed based on the final predictors.

Results: Overall, 86 out of 305 patients (28%) with infected necrotizing pancreatitis were successfully treated with antibiotics alone. Our final prediction model included presence of organ failure at the start of antibiotics [odds ratio (OR): 0.46, 95% CI: 0.22–0.99, $P = 0.046$], presence of central necrosis (OR: 0.11, 95% CI: 0.05–0.23, $P < 0.001$) and presence of subtotal necrosis (OR: 0.12, 95% CI: 0.03–0.36, $P < 0.001$). The area under the curve was 0.74 (95% CI: 0.70–0.75). The prognostic nomogram yielded a probability of successful antibiotic treatment of 5% when organ failure and central necrosis were present and 47% when all predictors were absent.

Conclusions: In patients with infected necrotizing pancreatitis, predictors negatively impacting successful treatment with antibiotics are organ failure at the start of antibiotics, and the presence of central or subtotal necrosis on imaging.

Key Words: antibiotics, infected necrotizing pancreatitis, Predictors

(*Ann Surg* 2025;282:860–867)

Acute pancreatitis is one of the most common gastrointestinal diseases requiring hospital admission.[1,2] The clinical course ranges from a mild, self-limited illness to a fulminant, life-threatening disease. Approximately 20% of patients with acute pancreatitis develop necrotizing pancreatitis.[3,4] In about 30% of these patients, secondary infection of the (peri)pancreatic necrosis occurs.[5,6] Typically, it takes up to 2 to 4 weeks to develop infected necrosis,

Received for publication February 21, 2025; accepted May 9, 2025.
From the *Department of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands; †Department of Research & Development, St. Antonius Hospital, Nieuwegein, The Netherlands; ‡Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands; §Department of Gastroenterology and Hepatology, Amsterdam UMC, Location University of Amsterdam, Amsterdam, The Netherlands; ‖Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands; ¶Department of Surgery, Amsterdam UMC, Location University of Amsterdam, Amsterdam, The Netherlands; #Department of Medical Microbiology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; **Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; ††Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht, The Netherlands; ‡‡Department of Surgery, Maastricht UMC+, Maastricht, The Netherlands; §§School of Nutrition and Translation Research in Metabolism (NUTRIM), Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands; ‖‖Department of Radiology, St. Antonius Hospital, Nieuwegein, The Netherlands; ¶¶Department of Medical Microbiology and Infection Prevention, Amsterdam UMC, Location University of Amsterdam, Amsterdam, The Netherlands; ##Amsterdam Institute for Immunology and Infectious Diseases, Infectious diseases, Amsterdam, The Netherlands; ***Department of Gastroenterology, St. Antonius Hospital, Nieuwegein, The Netherlands; and †††Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands.
✉h.c.vansantvoort@antoniusziekenhuis.nl; ha.pauw@antoniusziekenhuis.nl.
Data are available upon reasonable request from the corresponding author.
H.C.T., L.B., and N.J.S. collected study data and revised the manuscript. H.S.P. collected study data, performed the statistical analysis, and drafted the manuscript. E.D. and L.A.D. provided statistical advice and revised the manuscript. T.L.B. reviewed abdominal radiologic images. R.P.V., M.G.B., S.A.B., J.E.v.H., F.F.v.d.B., R.V., and H.C.v.S. co-authored the writing of the manuscript.
The authors report no conflicts of interest.
Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.
Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.
DOI: 10.1097/SLA.0000000000006902

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

but more rarely it can also occur in the early phase of acute pancreatitis.[7] Infected necrotizing pancreatitis carries a relatively poor prognosis, with a 15% to 35% mortality rate, in contrast to a 0% to 1% mortality rate in mild acute pancreatitis.[8]

Current treatment guidelines for infected necrotizing pancreatitis recommend treatment according to the step-up approach.[7,9,10] The first step is to initiate intravenous antibiotic treatment. If no clinical improvement or even deterioration is observed after starting antibiotics, the subsequent step consists of percutaneous or endoscopic drainage of the infected collection. If needed, drainage can be followed by various options for pancreatic debridement (eg, endoscopic or surgical). Invasive interventions were always considered imperative in the treatment of infected necrotizing pancreatitis; however, the optimal timing remained unclear. The recent POINTER trial demonstrated that immediate drainage, as compared with postponed drainage, had no benefits in terms of complications or survival.[11] Interestingly, when postponing drainage, 19 out of 49 patients (39%) did not require invasive intervention and were successfully treated with antibiotics alone.[11] Previous retrospective observational studies reported lower success rates for antibiotic treatment alone.[12–17] Predicting which patients could be effectively treated with antibiotics alone would be of important value for counseling patients, for clinical decision-making and for stratification in clinical studies.[12–18] We therefore aimed to develop a clinical prediction model for successful treatment of infected necrotizing pancreatitis with antibiotics alone.

METHODS

Study Design and Population

This post hoc analysis included patients from the Dutch nationwide prospective registry of acute pancreatitis (PWN-CORE). A subset of patients was also included in the randomized POINTER trial.[11] For the current study, all patients aged over 18 years with necrotizing pancreatitis in whom antibiotics were started for suspected or proven infected necrosis, treated between January 1, 2010, and December 31, 2019, were selected in 22 participating Dutch hospitals. Patients with incomplete data regarding antibiotic treatment were excluded. Other exclusion criteria were patients with chronic pancreatitis according to the M-ANNHEIM criteria or pancreatic carcinoma at admission.[19]

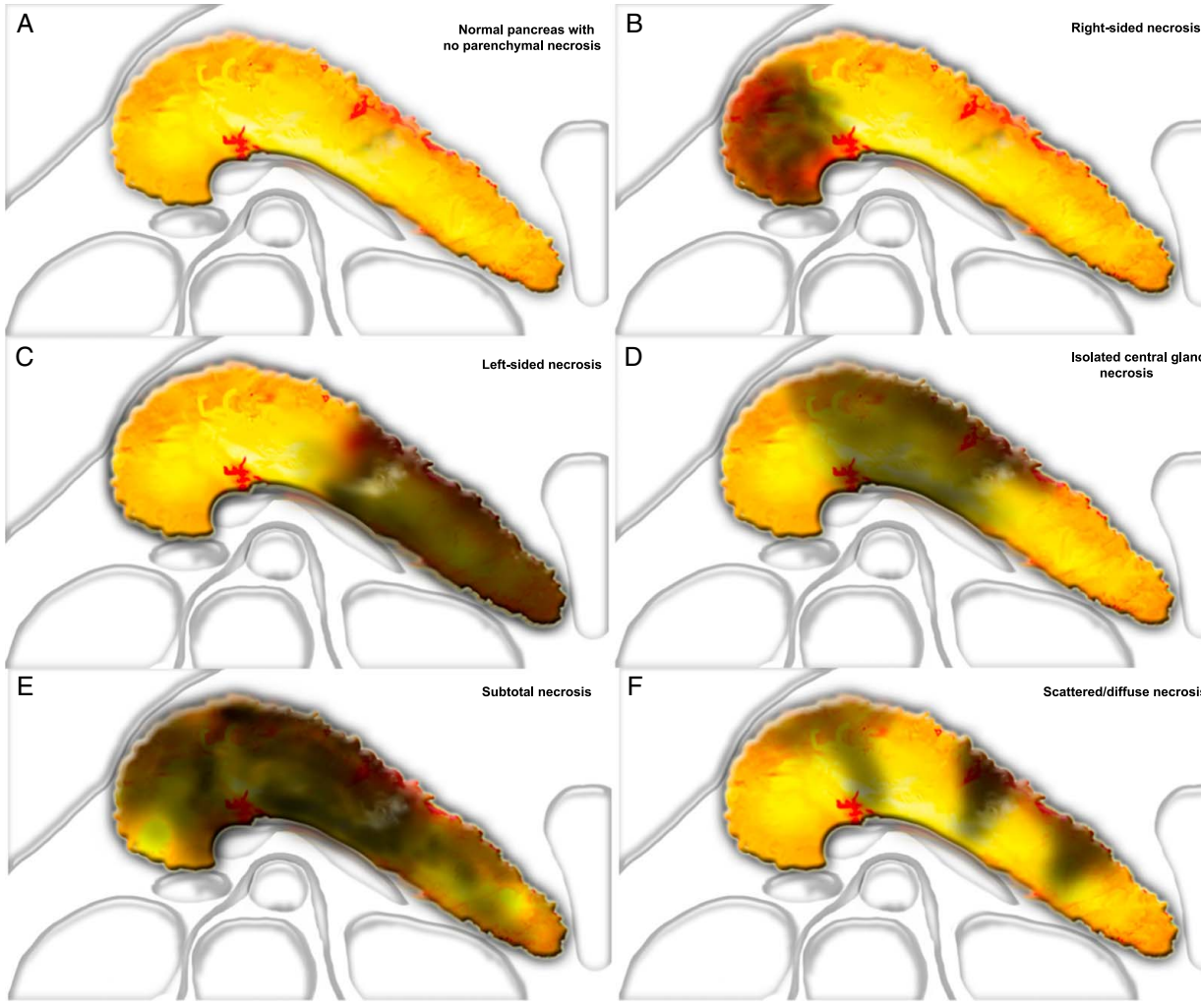

FIGURE 1. Patterns of pancreatic necrosis. A, Normal pancreas with no parenchymal necrosis. B, Right-sided necrosis. C, Left-sided necrosis. D, Isolated central gland necrosis. E, Subtotal necrosis. F, Scattered/diffuse necrosis.

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

From the POINTER trial, we only included patients from the postponed drainage arm, as our aim was to investigate successful treatment with antibiotics alone. The ethical review board approved the PWN-CORE registration cohort and the POINTER trial (NL52361.018.15). This study was reported according to the "Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis" (TRIPOD+AI) guidelines and conducted in accordance with the principles of the Declaration of Helsinki.[20] All patients or their legal representative gave written informed consent.

Definitions and Treatment

Acute pancreatitis was defined according to the revised Atlanta criteria.[3] Necrotizing pancreatitis was defined as necrosis of the pancreatic parenchyma or extrapancreatic necrosis without pancreatic parenchymal necrosis (EXPN), demonstrated on contrast-enhanced computed tomography (CT).[3] Pancreatic parenchymal necrosis was defined as diffuse or focal area(s) of non-enhancing pancreatic parenchyma as detected on CT. EXPN was defined as heterogeneous non-liquefied material on CT in the absence of pancreatic parenchymal non-enhancement.

An expert radiologist (T.L.B.), blinded to the outcome, reviewed all abdominal CT images to assess the presence, pattern, and extent of the (peri)pancreatic necrosis, the CT-severity index (CTSI), and the presence of gas in these collections. The extent of pancreatic necrosis was divided into no parenchymal necrosis, $<30\%$, 30% to 50% or $>50\%$.[21] The pattern of parenchymal necrosis was categorized based on the anatomical location (ie, right, left, subtotal, central, or diffuse, Fig. 1).

Diagnosis timing for (suspected) infected necrotizing pancreatitis was based on days from admission to antibiotic initiation. Proven infected necrosis was defined as (1) the presence of gas in a collection with (peri)pancreatic necrosis on CT and/or (2) a positive culture from fine-needle aspiration (FNA) or from a drainage procedure from a (peri)pancreatic collection/walled-off necrosis. Organ failure at start of antibiotic treatment was defined as the presence of organ failure within 24 hours before antibiotic treatment. All definitions used are provided in Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F608.

Treatment of infected necrosis was performed according to the step-up approach.[7,10,22,23] The decision to step-up treatment after initial antibiotic therapy was made by the treating clinicians. In the Netherlands, this typically follows the protocol established in the PANTER trial, which recommends intervention (eg, catheter drainage, additional drain placement, upsizing of drains, or necrosectomy) in the absence of clinical improvement after ~72 hours of antibiotic therapy.[24] The POINTER trial randomized 1:1 between immediate drainage and postponed drainage.[11] Postponed catheter drainage included treatment with broad-spectrum antibiotics and supportive treatment, aimed to postpone drainage procedures until the collection with (peri)pancreatic necrosis became walled-off.

Study Outcome

The primary outcome was successful treatment of (suspected) infected necrotizing pancreatitis with antibiotics alone, meaning no invasive intervention (ie, image-guided percutaneous drainage, endoscopic trans-luminal drainage, and/or endoscopic/surgical necrosectomy) was performed and no pancreatitis-related death occurred. Follow-up was 6 months after discharge from the index admission.

Data Collection

Clinical data were collected from medical records during initial hospital admission. Data regarding clinical outcomes such as interventions, organ failure, and mortality were collected from admission until the end

of follow-up. Follow-up data from hospitals transfers or readmissions to other hospitals were obtained.

Statistical Analysis

All data were analyzed using R (version 4.4.0). Descriptive data were reported as mean with SD when normally distributed, and as median with interquartile ranges (IQR) when not normally distributed. Categorical data were shown as frequencies and percentages.

Missing values were imputed using the multivariate imputation by chained equations (MICE) algorithm with predictive mean matching for continuous variables and proportional odds logistic regression (polr) model for categorical variables, and m was set at 50.[25–27] The assumption of MICE, for example, that the missing data are missing completely at random or missing at random, was checked.

We created a prediction model for predicting successful treatment with antibiotics alone using multivariable logistic regression analysis. Predictors for univariable logistic regression were selected based on baseline differences, theoretical grounds, and clinical expertise. The association between the predictive factors and successful treatment was first evaluated by univariable logistic regression and reported as odds ratios (ORs) with their 95% CI. Predictors potentially associated with successful treatment in the univariable regression analysis ($P<0.10$) were included in multivariable regression analysis. On the basis of clinical reasoning, variables could also be excluded. The ORs derived from the multivariable analysis are presented as adjusted ORs (aORs). Through backwards stepwise selection we created a final model with only statistically significant variables. Statistical significance was set at $P<0.05$.

To meet the assumptions of logistic regression analysis, multicollinearity was assessed through variance inflation factor (VIF). A VIF over 10 is considered problematic and identifies collinearity.[28] For including continuous variables, the assumptions of linearity in the logit was assessed. The last assumption of logistic regression, independence of errors, means that no cases of data should be related, was evaluated.

The discrimination of the model was assessed using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. An AUC of <0.60 reflects poor discrimination; 0.60 to 0.75, possibly helpful discrimination; and more than 0.75, clearly useful discrimination.[29] The Nagelkerke R^2 was also used to determine which percentage of the variation in events was explained by the selected predictors. The calibration of our model was assessed through the Hosmer-Lemeshow test.

On the basis of the final model a nomogram was designed containing the final predictors independently associated with successful antibiotic treatment. Points were awarded to a factor if it was associated with an increased success chance of antibiotic treatment.

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.
Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 1. Patients' Characteristics and Univariable Logistic Regression for Successful Treatment of Infected Necrotizing Pancreatitis With Antibiotics Alone

Patient and disease characteristics	N = 305	OR (95% CI)	*P*
Age in yrs (mean, SD)	59 (13)	1.00 (0.99–1.02)	0.69
Male sex, N (%)	186 (61)	0.91 (0.55–1.52)	0.71
Etiology, N (%)			
Biliary*	155 (51)	—	—
Alcohol	37 (12)	1.49 (0.67–3.09)	0.33
Other	113 (37)	1.02 (0.59–1.75)	0.95
ASA divided into categories, N (%)†			
1*	88 (29)	—	—
2	139 (46)	0.96 (0.52–1.79)	0.89
3+4	71 (23)	2.31 (1.19–4.56)	0.01
Medical history, N (%)			
Cardiovascular disease	145 (48)	1.30 (0.80–2.16)	0.30
Pulmonary disease	45 (15)	1.89 (0.96–3.61)	0.07
Chronic renal disease	14 (5)	1.02 (0.27–3.14)	0.98
Diabetes mellitus	39 (13)	1.15 (0.54–2.35)	0.70
Highest CRP <48 h of admission‡† (mg/L) (mean, SD)	283 (156)	0.92 (0.97–1.02)	0.06
Highest leukocytes <48 h of admission† (10^9/L) (mean, SD)	18 (7)	0.95 (0.92–0.99)	0.01
CRP at start antibiotics ‡† (mg/L) (mean, SD)	231 (108)	0.93 (0.97–1.03)	0.20
Presence of organ failure at start antibiotics, N (%)†	61 (20)	0.50 (0.23–0.97)	0.05
FNA, yes, N (%)	56 (18)	0.65 (0.31–1.25)	0.22
Type empirical antibiotics started for IPN, N (%)			
Carbapenems*	123 (40)	—	—
Piperacillin/tazobactam	33 (11)	1.12 (0.45–2.61)	0.79
Cephalosporins/ metronidazole	95 (31)	1.38 (0.75–2.51)	0.28
Penicillins	36 (12)	1.32 (0.57–2.94)	0.51
Other	17 (6)	1.25 (0.37–3.66)	0.70
Imaging severity parameters			
CTSI (mean, SD)	6 (2)	0.69 (0.60–0.79)	<0.001
Presence of parenchymal necrosis, N (%)			
Parenchymal necrosis*	207 (68)	—	—
EXPN only	98 (32)	4.66 (2.74–8.02)	<0.001
Extent necrosis, N (%)			
No parenchymal necrosis*	98 (32)	—	—
<30%	98 (32)	0.38 (0.20–0.68)	0.001
30%–50%	51 (17)	0.17 (0.06–0.38)	<0.001
>50%	58 (19)	0.10 (0.03–0.25)	<0.001
Pattern parenchymal necrosis, N (%)			
Right	7 (2)	1.94 (0.37–9.00)	0.39
Left	15 (5)	1.02 (0.27–3.14)	0.98
Subtotal	97 (32)	0.18 (0.04–0.52)	0.006
Central	38 (12)	0.14 (0.06–0.30)	<0.001
Diffuse	50 (15)	1.91 (1.00–3.57)	0.05
Gas on CT, N (%)	107 (35)	1.13 (0.67–1.90)	0.63

*Reference category.
†Variable with imputed values.
‡per 50 units increase.
ASA indicates American Society of Anesthesiologists; CRP, c-reactive protein; CTSI, Computed Tomography severity index; CT, computed tomography; EXPN, extrapancreatic necrosis without pancreatic parenchymal necrosis; FNA,fine needle aspiration; IPN, infected pancreatic necrosis; N, number.

RESULTS

Overall, 305 patients were included, of whom 256 from the prospective PWN-CORE cohort (enrolled between 2010 and 2019) and 49 from the postponed drainage arm of the POINTER trial (enrolled between 2015 and 2019), see flowchart (Supplementary Figure 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F608). The primary outcome, successful treatment with antibiotics alone, occurred in 86 of 305 patients (28%). Antibiotics were started at a median of 17 days (IQR: 19) after admission and at initiation of antibiotics 15% of patients were admitted at the intensive care unit. In 25% of all patients, initial antibiotic therapy was administered for an indication other than infected pancreatic necrosis. Additional information is provided in the Supplementary appendix 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F608. Four patients (1%) suffered a pancreatitis-related death without any intervention performed. When an intervention was performed, the median interval between antibiotic initiation and first intervention was 10 days (IQR 20). Additional information regarding the patients who underwent an intervention is provided in Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/SLA/F608. Proven infected necrosis occurred in 201 patients (66%). Of these, 56 patients (28%) exhibited gas configurations on CT, 94 patients (47%) had a positive pancreatic culture, and 51 patients (25%) demonstrated both findings.

The following variables were associated with successful treatment with antibiotics in the univariable analysis: highest c-reactive protein (CRP) within 48 hours of admission (OR: 0.92, 95% CI: 0.97–0.99, $P = 0.06$), highest leukocytes within 48 hours of admission (OR: 0.95, 95% CI: 0.92–0.99, $P = 0.01$), presence of organ failure at start antibiotics (OR: 0.50, 95% CI: 0.23–0.97, $P = 0.05$), CTSI (OR: 0.69, 95% CI: 0.60–0.79, $P < 0.001$), EXPN only (OR: 4.66, 95% CI: 2.74–8.02, $P < 0.001$), presence of central gland necrosis (OR: 0.14, 95% CI: 0.05–0.22, $P < 0.001$), presence of subtotal necrosis (OR: 0.18, 95% CI: 0.04–0.52, $P = 0.006$), and presence of diffuse necrosis (OR: 1.91, 95% CI: 1.00–3.57, $P = 0.05$) (Table 1). The categorical variable extent of necrosis with no parenchymal necrosis as reference category was also statistically significant for each category (Table 1). The variables FNA (OR: 0.65, 95% CI: 0.31–1.25, $P = 0.22$) and type of empirical antibiotics did not show a significant association with the treatment with antibiotics alone. Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/SLA/F608 shows univariable logistic regression before imputation.

In multivariable analysis the following variables remained negatively associated with successful antibiotic treatment: presence of organ failure at the start of antibiotics (aOR: 0.46, 95% CI: 0.22–0.99, $P = 0.05$), presence of central necrosis (aOR: 0.11, 95% CI: 0.05–0.23, $P < 0.001$) and presence of subtotal necrosis (aOR: 0.12, 95% CI: 0.03–0.36, $P < 0.001$) (Table 2). The Nagelkerke R^2 was 0.25. The Hosmer-Lemeshow test showed a *P*-value of 0.92 indicating a good fit of the model. The AUC of the ROC curve was 0.75 (95% CI: 0.69–0.80) (Supplementary Figure 2, Supplemental Digital Content 1, http://links.lww.com/SLA/F608). All included variables had a VIF close to 1 (Supplementary Table 4, Supplemental Digital Content 1, http://links.lww.com/SLA/F608). In addition, we also performed a post hoc multivariable analysis with extent of necrosis instead of necrosis patterns (Supplementary Table 5, Supplemental Digital Content 1, http://links.lww.com/SLA/F608).

In the nomogram, a total score of 227 points – reflecting absence of organ failure, central gland necrosis, and subtotal

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 2. The Final Model for Predicting Successful Treatment With Antibiotics Alone in Infected Necrotizing Pancreatitis Patients: Multivariable Logistic Regression Analysis

Predictor	Estimate (β)	aOR (95% CI)	*P*
Constant	−0.10	0.90	
Presence of organ failure at start antibiotics	−0.71	0.46 (0.22–0.99)	0.046
Central gland necrosis	−2.21	0.11 (0.05–0.23)	< 0.001
Subtotal necrosis	−2.11	0.12 (0.03–0.36)	< 0.001

AUC 0.75 (95% CI 0.69–0.80).
Nagelkerke $R^2 = 0.25$.

necrosis – corresponded to a 47% probability of successful antibiotic treatment. In contrast, the presence of organ failure and central gland necrosis reduced this probability to 5% (Fig. 2).

DISCUSSION

This nationwide study determined clinical and radiologic predictors for successful treatment with antibiotics alone in 305 patients with infected necrotizing pancreatitis. We found that one clinical, the presence of organ failure at start of antibiotics, and 2 radiologic variables, the presence of subtotal or central gland necrosis, were negatively associated with successful treatment with antibiotics alone.

Previously, 2 very small retrospective observational studies identified successfully treated patients with antibiotics alone and performed analyses that showed differences in severity prediction scores (eg, CTSI score, APACHE II) and laboratory values.[12,13] Several other studies also reported small numbers of patients but due to the lack of detailed comparative patient characteristics, a direct comparison with our study data was not possible.[14–18] Only one study performed univariable analysis to assess predictors, identifying significant differences in the modified Glasgow score, CTSI score, hemoglobin, albumin, and CRP level.[12] Our cohort showed comparable predictors in univariable analyses regarding the variables CRP level at start of antibiotics and CTSI score. Interestingly, in the present study, only one clinical variable – the presence of organ failure at the start of antibiotics – remained associated with successful treatment in the multivariable analysis. This may reflect clinicians' tendency to intervene early in patients with organ failure, a sign of severe clinical condition, and thus may represent confounding by indication.[3,30] In addition, organ failure is also associated with mortality in acute pancreatitis, which could also explain its negative association with successful treatment. Our findings are in line with another study identifying organ failure as a negative predictor for successful percutaneous catheter drainage only (ie, survival without need for necrosectomy) in infected necrotizing pancreatitis.[31]

The presence of subtotal or central gland necrosis was strong negative predictors. If one of these diagnostic criteria is present, the main pancreatic duct is usually affected and with still some viable pancreatic tissue in the pancreatic tail, this results in continuous extraductal and extrapancreatic leakage of pancreatic fluids. Such leakage may represent an early consequence of disrupted pancreatic duct syndrome, a condition in which it has been suggested that conservative treatment is often insufficient.[32–35] This could explain why

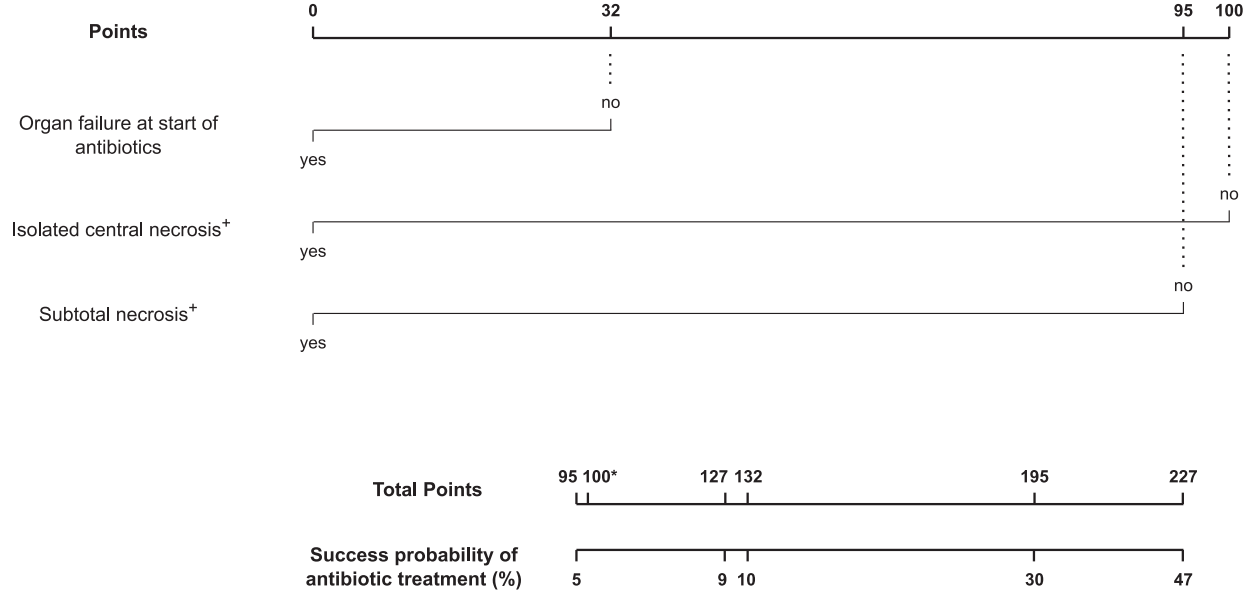

FIGURE 2. Nomogram for the success probability of antibiotic treatment in infected necrotizing pancreatitis. When absent each predictor is awarded points (32, 95, 100). The sum of the 3 predictors lies between 95 and 227 points and can be found on the 'Total points' line. The points on this line corresponds with a success chance ranging from 5% to 47%. +Only one of these predictors can be present in a patient, resulting in a minimum of 95 points. *Because of rounding, 100 points also represents a 5% probability.

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.
Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

antibiotic treatment alone frequently fails in patients with subtotal or central gland necrosis. Also, this theory supports our finding from univariable analysis that patients with EXPN alone have a higher change of being successfully treated with antibiotics alone. On the basis of our findings, we propose standardizing the identification and classification of parenchymal necrosis by location (Fig. 1), as it may reliably predict the clinical course in patients with infected necrotizing pancreatitis.

Our study has several limitations. First, we performed a post hoc analysis of 2 cohorts, one comprising of patients randomized in a multicenter trial. Although our cohort is unique in its size and the range of variables included, the predefined factors were limited by data availability. Although we incorporated detailed predictors known to indicate disease severity (eg, CRP, CTSI), it is possible that other relevant variables not captured in our database also hold predictive value. Second, our model lacks external validation and this should be performed in other, preferably prospective, cohorts of equal or larger size. Third, we determined that the days from admission to start antibiotics best reflects the timing of diagnosis for (suspected) infected necrotizing pancreatitis. This determination is based on the first step of the step-up approach, which involves starting antibiotics when infection is suspected. In our cohort, the median time to start antibiotics was 17 days after admission, slightly earlier than other studies who reported a median of 29 days and 30 days of diagnosis of infected necrotizing pancreatitis.[4,36] This difference may be attributed to the inclusion of patients diagnosed with infection based on clinical suspicion. Some patients may have had sterile necrosis, but without intervention, infection cannot be proven. This aligns with daily clinical practice, where infected necrosis is rarely proven before invasive intervention and the decision to perform invasive intervention is often based on clinical suspicion on infected necrosis (ie, persistent sepsis or progressive clinical deterioration despite maximal support). Using this strategy, previous studies by the Dutch Pancreatitis Study Group confirmed suspected infected necrosis as proven infected necrosis based on culture results from intervention in 87% to 91% of patients.[11,24]

Fourth, the decision to consider antibiotic treatment unsuccessful and to proceed with the step-up approach was made at the discretion of the treating clinicians. Although we assume that most clinicians in the Netherlands generally adhere to the standard step-up protocol as described in the Dutch PANTER trial – initiating intervention within 72 hours in the absence of clinical improvement – our data suggest that, in current practice, this timeline is often somewhat more delayed.[24] This variation is inherent to the retrospective nature of the study but also reflects real-world clinical decision-making. The strengths of this study are the multicenter design of this study, because it ensures a representative sample of the Dutch patient population, supported by baseline characteristics and radiologic parameters similar to those in previous studies.[37,38] Compared with other studies, our larger cohort size allows for investigation of more predictive factors, including detailed radiologic variables. We evaluated only factors available before outcome measurement and commonly used in routine clinical practice, as these factors can be used for future stratification or patient identification for research and prognostication in daily clinical practice. For example, the nomogram developed in this study can facilitate clinical decision-making for treating infected necrotizing pancreatitis and improve communication with patients and their families about the likelihood of treatment success. This nomogram could particularly be valuable for determining the optimal timing for invasive interventions. For instance, if a patient with infected necrotizing pancreatitis shows organ failure and central gland necrosis at the start of antibiotics, the very low likelihood of success with antibiotics alone may prompt the clinician to consider a more urgent intervention.

Antibiotic stewardship is increasingly important in infectious diseases and is also warranted in the management of acute pancreatitis.[39] With better better-targeted antimicrobial therapy, an even greater proportion of patients with infected necrosis could potentially be treated with antibiotics alone. This may require a return to more widespread use of FNA in these patients. Antibiotic stewardship, including FNA and procalcitonin measurements to guide decision-making is currently investigated by the Dutch pancreatitis Study Group is the nationwide PIANO study (NL-OMON56749).[40]

In conclusion, in patients with suspected or proven infected necrotizing pancreatitis, the presence of organ failure at the start of antibiotics, the presence of central necrosis and the presence of subtotal necrosis are negative predictors for successful treatment with antibiotics alone. Our clinical prediction model and nomogram have high potential for counseling and guiding clinical decision in the management of patients with infected necrotizing pancreatitis.

ACKNOWLEDGMENTS

The authors thank Martyn Stott for reviewing the manuscript for grammar and style.

REFERENCES

1. Spanier BWM, Bruno M, Dijkgraaf M. An update on hospital admissions for acute pancreatitis in the Netherlands (2013–2019). *Eur J Gastroenterol Hepatol*. 2022;34:726–727.
2. Iannuzzi JP, King JA, Leong JH, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. *Gastroenterology*. 2022;162:122–134.
3. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.
4. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*. 2011;141:1254–1263.
5. Bugiantella W, Rondelli F, Boni M, et al. Necrotizing pancreatitis: a review of the interventions. *Int J Surg*. 2016;28: S163–S171.
6. Wolbrink DRJ, Kolwijck E, Ten Oever J, et al. Management of infected pancreatic necrosis in the intensive care unit: a narrative review. *Clin Microbiol Infect*. 2020;26:18–25.
7. Working Group IAP/APA Acute Pancreatitis Guidelines IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology*. 2013;13:e1–e15. doi:10.1016/j.pan.2013.07.063
8. van Dijk SM, Hallensleben NDL, van Santvoort HC, et al. Acute pancreatitis: recent advances through randomised trials. *Gut*. 2017;66:2024–2032.
9. Crockett SD, Wani S, Gardner TB, et al. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. *Gastroenterology*. 2018;154: 1096–1101.

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

10. Leppäniemi A, Tolonen M, Tarasconi A, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. *World J Emerg Surg*. 2019;14:27.
11. Boxhoorn L, van Dijk SM, van Grinsven J, et al. Immediate versus postponed intervention for infected necrotizing pancreatitis. *N Engl J Med*. 2021;385:1372–1381.
12. Al-Sarireh B, Mowbray NG, Al-Sarira A, et al. Can infected pancreatic necrosis really be managed conservatively? *Eur J Gastroenterol Hepatol*. 2018;30:1327–1331.
13. Sivasankar A, Gounder Kannan D, Ravichandran P, et al. Outcome of severe acute pancreatitis: is there a role for conservative management of infected pancreatic necrosis? *Hepatobiliary Pancreat Dis Int*. 2006;5:559–604.
14. Rasslan R, da Costa Ferreira Novo F, Rocha MC, et al. Pancreatic necrosis and gas in the retroperitoneum: treatment with antibiotics alone. *Clinics*. 2017;72:87–94.
15. Oláh A, Belágyi T, Bartek P, et al. Alternative treatment modalities of infected pancreatic necrosis. *Hepatogastroenterology*. 2006;53:603–607.
16. Runzi M, Niebel W, Goebell H, et al. Severe acute pancreatitis: nonsurgical treatment of infected necroses. *Pancreas*. 2005;30:195–199.
17. Garg PK, Sharma M, Madan K, et al. Primary conservative treatment results in mortality comparable to surgery in patients with infected pancreatic necrosis. *Clin Gastroenterol Hepatol*. 2010;8:1089–1094.e2.
18. Lee JK, Kwak KK, Park JK, et al. The efficacy of nonsurgical treatment of infected pancreatic necrosis. *Pancreas*. 2007;34:399–404.
19. Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. *J Gastroenterol*. 2007;42:101–119.
20. Collins GS, Moons KGM, Dhiman P, et al. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. *BMJ*. 2024;385:e078378.
21. Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: value of CT in establishing prognosis. *Radiology*. 1990;174:331–336.
22. Yokoe M, Takada T, Mayumi T, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. *J Hepatobiliary Pancreat Sci*. 2015;22:405–432.
23. Arvanitakis M, Dumonceau J-M, Albert J, et al. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. *Endoscopy*. 2018;50:524–546.
24. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010;362:1491–1502.
25. Jakobsen JC, Gluud C, Wetterslev J, et al. When and how should multiple imputation be used for handling missing data in randomised clinical trials—a practical guide with flowcharts. *BMC Med Res Methodol*. 2017;17:162.
26. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. *Prev Sci*. 2007;8:206–213.
27. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338(jun29 1):b2393–b2393.
28. Field A, Miles J, Field Z. *Discovering Statistics Using R*. SAGE Publications; 2012.
29. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and calibration of clinical prediction models. *JAMA*. 2017;318:1377.
30. Vege SS, Chari ST. Organ failure as an indicator of severity of acute pancreatitis: time to revisit the Atlanta classification. *Gastroenterology*. 2005;128:1133–1135.
31. Hollemans RA, Bollen TL, van Brunschot S, et al. Predicting success of catheter drainage in infected necrotizing pancreatitis. *Ann Surg*. 2016;263:787–792.
32. van Dijk SM, Timmerhuis HC, Verdonk RC, et al. Treatment of disrupted and disconnected pancreatic duct in necrotizing pancreatitis: a systematic review and meta-analysis. *Pancreatol Off J Int Assoc Pancreatol*. 2019;19:905–915.
33. Jang JW, Kim M-H, Oh D, et al. Factors and outcomes associated with pancreatic duct disruption in patients with acute necrotizing pancreatitis. *Pancreatology*. 2016;16:958–965.
34. Chong E, Ratnayake CB, Saikia S, et al. Endoscopic transmural drainage is associated with improved outcomes in disconnected pancreatic duct syndrome: a systematic review and meta-analysis. *BMC Gastroenterol*. 2021;21:87.
35. Sandrasegaran K, Tann M, Jennings SG, et al. Disconnection of the pancreatic duct: an important but overlooked complication of severe acute pancreatitis. *RadioGraphics*. 2007;27:1389–1400.
36. Timmerhuis HC, van den Berg FF, Noorda PC, et al. Over- and misuse of antibiotics and the clinical consequence in necrotizing pancreatitis: an observational multicenter study. *Ann Surg*. 2023;278:e812–e819.
37. van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. *Lancet*. 2018;391:51–58.
38. Boxhoorn L, Verdonk RC, Besselink MG, et al. Comparison of lumen-apposing metal stents versus double-pigtail plastic stents for infected necrotising pancreatitis. *Gut*. 2023;72:66–72.
39. van Santvoort H, Voermans RP, Zyromski NJ, et al. Antibiotic stewardship in acute pancreatitis. *Br J Surg*. 2025;112:znaf007.
40. Siriwardena AK, Jegatheeswaran S, Mason JM, et al. A procalcitonin-based algorithm to guide antibiotic use in patients with acute pancreatitis (PROCAP): a single-centre, patient-blinded, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2022;7:913–921.

DISCUSSANTS

Rifat Latifi (Tucson, Arizona, USA)

I would like to thank the ESA for the honor of discussing the paper by Prof Dr Hjalmar C. van Santvoort's group, which provides an important investigation into the management of infected necrotizing pancreatitis using antibiotics alone. The study effectively explores predictors of successful outcomes through a multivariable logistic regression model. I also want to congratulate the presenter on an excellent presentation. The research methodology is robust, utilizing a large cohort of patients drawn from a nationwide prospective database. Although surgeons have traditionally believed that patients with multiple organ failure and complicated pancreatitis may ultimately require some form of endoscopic or surgical intervention, this study offers clear evidence regarding which patients may respond positively to antibiotics alone. Notably, only 28% of the patients achieved successful treatment with antibiotics, underscoring the complexity of the disease. The authors identify several significant predictors of treatment success, namely the presence of organ failure, central gland necrosis, and subtotal necrosis, which align with existing literature while also providing new insights into the clinical decision-making process. The use of a nomogram to estimate probabilities of success based on these predictive variables represents a practical tool for future clinical applications. Although the results contribute valuable insights for the management of infected pancreatitis, the overall success rate of treatment with antibiotics alone raises questions about the necessity for earlier interventions in patient care protocols. In summary, this study meticulously outlines significant clinical markers predictive of antibiotic treatment success in infected necrotizing pancreatitis, offering evidence

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.
Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

that could enhance clinical decision-making and patient counseling, while inviting further discussions on management strategies for this critical condition. I have 3 questions:

First, it would be useful to know the etiology of acute pancreatitis in the study population, as it may influence treatment strategies and outcomes. At what point did the authors (or treating clinicians) declare the antibiotic treatment to be unsuccessful before proceeding with the step-up approach, and what specific criteria were used to make this determination?

Second, could the authors please provide insights into the outcomes of patients who did not respond to antibiotic treatment, including the complications they experienced and the types of interventions they ultimately required? In addition, did continuing antibiotic therapy merely delay, rather than prevent, the need for surgical, endoscopic, or drainage procedures?

Finally, in the context of drainage procedures for infected necrotizing pancreatitis from a (peri)pancreatic collection or walled-off necrosis, could you clarify the success rates of these interventions, specifically how many patients required further surgical procedures after the initial drainage?

Again, congratulations to the authors on this insightful study addressing one of the most challenging aspects of acute pancreatitis management. Your work significantly contributes to our further understanding of the role of antibiotic treatment in infected necrotizing pancreatitis.

Response From Hannah S. Pauw (Nieuwegein, The Netherlands)

Thank you for your comments and for reviewing our paper. First, we also looked at the etiology of acute pancreatitis patients, and the most common etiology was a biliary cause. Naturally, the underlying etiology is treated accordingly, for example, by performing a laparoscopic cholecystectomy in biliary pancreatitis or advising alcohol abstinence in alcohol-induced pancreatitis. In the Netherlands, the in-hospital management of pancreatitis is generally the same across all hospitals. As such, in our opinion, it does not influence the outcome in this population. When we declared that the antibiotic treatment was unsuccessful, it was at the discretion of the treating physician. In general, in the Netherlands, we adhere to the "step-up approach", as described in the PANTER study, which states that, when you see no improvement or even deterioration after 72 hours, you should opt for an intervention. However, we observed that the time between the initiation of antibiotics and the eventual intervention slightly exceeded 10 days. As you know, in clinical practice, protocols are not always followed to the letter, but this timeframe was generally used to determine when antibiotic therapy was considered unsuccessful.

Second, regarding the outcomes of patients who did not respond to antibiotic treatment, we included a supplementary table, Supplemental Digital Content 1, http://links.lww.com/SLA/F608 in our manuscript detailing the characteristics of this subgroup and the interventions performed. Of the 219 patients for whom antibiotic therapy was unsuccessful, 216 eventually underwent an intervention, as 3 patients died before any intervention could be performed. Among these, 31% underwent endoscopic necrosectomy, whereas 18% required surgical necrosectomy after initial percutaneous or endoscopic drainage. It is difficult to determine whether continued antibiotic treatment delayed definitive intervention, as we lack a comparison cohort to assess the time interval between antibiotic initiation and intervention. Comparing this timing across other cohorts would indeed be valuable to better understand any potential delay.

Finally, 63% of patients required percutaneous drainage, and 98 ultimately underwent additional necrosectomy, 18% of which were surgical. Although this is a high proportion, it likely reflects the underlying severity of the disease.

Pierre-Alain Clavien (Zurich, Switzerland)

Thank you, Dr van Santvoort for this clinically relevant paper. I have 2 questions: First, was every patient with necrosis treated with antibiotics or did you treat some without antibiotics, and if so, why? Second, were the same antibiotics always used? If not, this could be a significant bias, as we may miss 30% of the bacteria with Ciprofloxacin, for example.

Response From Hannah S. Pauw (Nieuwegein, The Netherlands)

Thank you for your questions and important remarks. All patients were treated with antibiotics in this study. We also looked at the types of antibiotics used, and this is also stated in the manuscript. It varied between the patients. Most of them had one of the 3 most common antibiotic regimes in the Netherlands, but it differed from patient to patient. In other words, not all patients received the same antibiotics.

Léo H Bühler (Fribourg, Switzerland)

I think that the term "necrosis" is incorrect. What the radiologists call necrosis is an absence of blood flow, but, for some of these patients, the pancreas recovered after 6 to 12 months. So, this is not really necrosis. What do you think?

Response From Hannah S. Pauw (Nieuwegein, The Netherlands)

In some of the patients, the extent of the necrosis sometimes varied, as what initially seemed like necrosis later turned out to be edema. This highlights the importance of timing when performing imaging. A CT scan should ideally be done after the first 72 hours, as scans performed within 72 hours are more likely to show inflammation and edema rather than true necrosis. In our study, we saw that after subtotal necrosis, patients did not have much pancreas left. However, this finding can vary significantly across cohorts and is heavily influenced by the quality of imaging and the experience of the radiologist assessing it. In this cohort, repeated imaging was performed to help distinguish between necrosis and edema, and all scans were reassessed by an expert pancreatic radiologist, which added a level of diagnostic consistency and reliability.

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.