図 15: 重症の胆管炎に使用する抗菌薬　1 例目

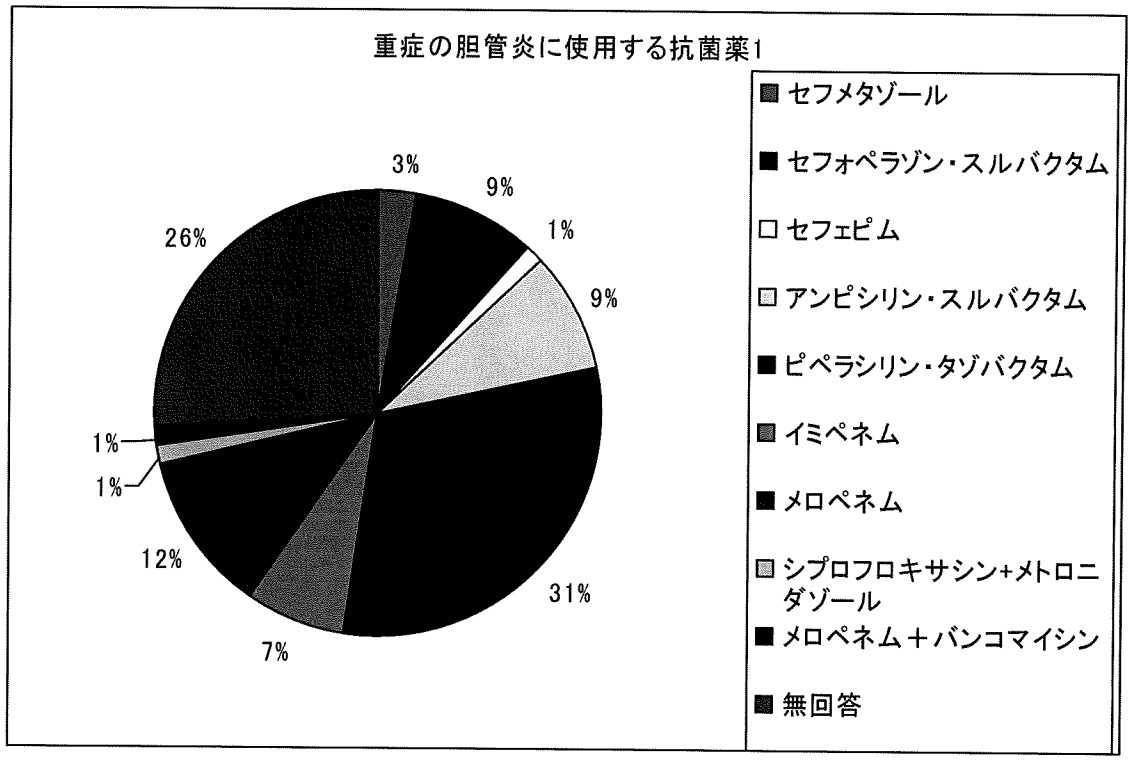
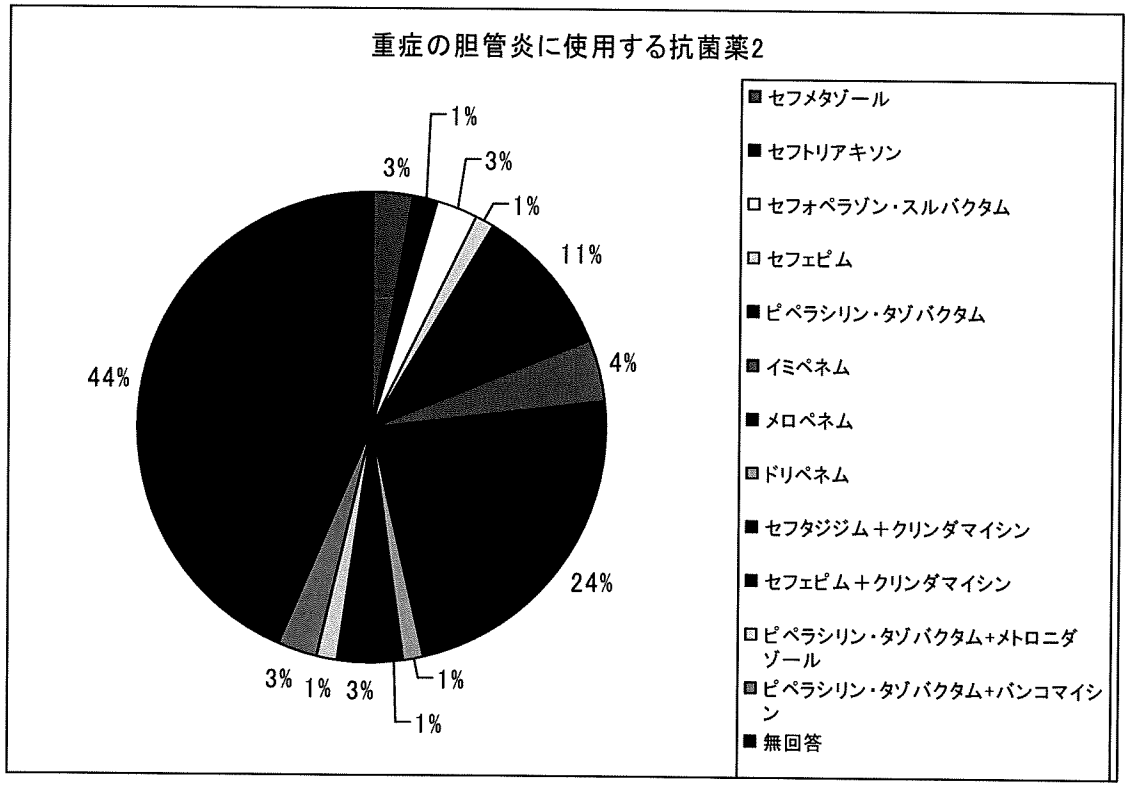


図 16: 重症の胆管炎に使用する抗菌薬　2 例目



平成21年度厚生労働省科学研究費補助金（地域医療基盤開発推進研究事業）
分担研究報告書

国内版、国際版急性胆道炎診療ガイドラインの普及と、日本と世界の実地診療・健康アウトカム等に与える影響の検証に関する研究

分担研究　国際版急性胆道炎診療ガイドライン(Tokyo Guidelines)の検証－日本の臨床からの評価－

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【研究要旨】
【目的】国内版「科学的根拠に基づく急性胆管炎・胆嚢炎の診療ガイドライン」と、国際版ガイドライン「Tokyo Guidelines for the management of acute cholangitis and cholecystitis」における診断基準・重症度判定基準が実際の臨床において、どのように用いられるか評価し、その診断特性や有効性、問題点を検討する。
【対象】2004年11月～2005年11月までの症例を対象として、名古屋第二赤十字病院における過去の急性胆管炎症例、急性胆嚢炎症例をretrospectiveに検証し、実臨床における検討を行った。
【方法】・診療担当医が「急性胆管炎」または「急性胆嚢炎」と診断した症例を対象とした。
・初期診断が急性胆管炎または急性胆嚢炎であった症例が、ガイドラインの診断基準において、どのように診断されるのか、また、重症度の分布はどうなるのかを検討した。
・最終診断からみて、ガイドラインの診断基準の正診率について検討した。
・国内版・国際版ガイドラインの感度・特異度を検討して診断基準の診断特性を検証した。
【結果】
＜国内版ガイドライン＞急性胆管炎：疑診＋確診の感度は83.6%、特異度は30.8%、確診のみの感度は45.9%、特異度は84.6%であった。急性胆嚢炎：疑診＋確診の感度は89.0%、特異度は37.5%、確診のみの感度は72.6%、特異度は62.5%であった。
＜Tokyo Guidelines＞急性胆管炎：疑診＋確診の感度は72.1%、特異度は38.5%、確診のみの感度は63.9%、特異度は69.2%であった。急性胆嚢炎：確診のみの感度は84.9%、特異度は50.0%であった。
Charcot3徴の感度11.5%、特異度84.6%であった。Murphy徴候は20.5%、87.5%であった。
【結論】CharcotやMurphyが100年以上前に提唱した診断ツールは、特異度の面で優れているが、感度の面で劣っており、症例の拾い上げには感度を優先した診断ツールが必要である。その点で、現在のガイドラインは目的にかなったガイドラインの診断基準となっており、さらにGold Standardへ近づく上で特異度の改善が必要であると思われる。

A. 研究目的

国内版「科学的根拠に基づく急性胆管炎・胆嚢炎の診療ガイドライン」と、国際版ガイドライン「Tokyo Guidelines for the management of acute

cholangitis and cholecystitis」における診断基準・重症度判定基準が実際の臨床において、どのように診断され、重症度も判定されるのかを評価し、その診断特性や有効性、問題点を検討する。

B. 研究方法

名古屋第二赤十字病院における過去の急性胆管炎症例、急性胆嚢炎症例を retrospective に検証し、実臨床における検討を行った。

C. 研究結果

・初期診断がそのときの担当医により「急性胆管炎」と下した症例と、初期診断をそのとき担当医により「急性胆嚢炎」と下した症例を対象として種々の検討を行った。

・2004 年 11 月～2005 年 11 月までの症例を対象として、初期診断が急性胆管炎であった症例がガイドラインの診断基準において、疑診や確診など、どのような診断が診断基準により下されるのか、果たして、重症度の分布はどうなるのかを検討した。

・また、急性胆嚢炎症例でも同様の検討を行った。

・逆に最終診断からみて、ガイドラインの診断基準がどれくらいの正診率を得ているかについて検討した。

・結果、ガイドラインの検証として、国内版・国際版ガイドラインの感度・特異度などを検討して診断基準の診断特性を検証した。

・ガイドラインの普及という点では、研修医向けの勉強会や講演会でガイドラインの講義を行ったり、研修医向けの商業雑誌でガイドラインを解説したり、実例を用いての解説を行った。

・国内版ガイドライン

急性胆管炎：疑診＋確診の感度は 83.6%、特異度は 30.8%、確診のみの感度は 45.9%、特異度は 84.6%であった。

急性胆嚢炎：疑診＋確診の感度は 89.0%、特異度は 37.5%、確診のみの感度は 72.6%、特異度は 62.5%であった。

・Tokyo Guidelines

急性胆管炎：疑診＋確診の感度は 72.1%、特異度は 38.5%、確診のみの感度は 63.9%、特異度は 69.2%であった。

急性胆嚢炎：確診のみの感度は 84.9%、特異度は 50.0%であった。

Charcot3 徴の感度 11.5%、特異度 84.6%であった。

Murphy 徴候の感度 20.5%、特異度は 87.5%であった。

D. 考察

感度の面で、国内版ガイドラインも国際版 Tokyo Guidelines も従来の臨床診断に使用してきた Charcot3 徴や Murphy 徴候よりも優れていることがわかった。

E. 結論

Charcot や Murphy が 100 年以上前に提唱した診断ツールは、特異度の面で優れているが、感度の面で劣っており、症例の拾い上げには感度を優先した診断ツールが必要である。その点で、現在のガイドラインは目的にかなったガイドラインの診断基準となっており、さらに Gold Standard へ近づく上で特異度の改善が必要であると思われる。

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H. 知的財産権の出願・登録状況

1. 特許取得

   なし

2. 実用新案登録

   なし

3. その他

   なし

研究成果の刊行に関する一覧表

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Cutting-edge information for the management of acute pancreatitis

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Abstract Considering that the Japanese (JPN) guidelines for the management of acute pancreatitis were published in Takada et al. (J HepatoBiliary Pancreat Surg 13:2–6, 2006), doubts will be cast as to the reason for publishing a revised edition of the Guidelines for the management of acute pancreatitis: the JPN guidelines 2010, at this time. The rationale for this is that new criteria for the severity assessment of acute pancreatitis were made public on the basis of a summary of activities and reports of shared studies that were conducted in 2008. The new severity classification is entirely different from that adopted in the 2006 guidelines. A drastic revision was made in the new criteria. For example, about half of the cases that have been assessed previously as being 'severe' are assessed as being 'mild' in the new criteria. The JPN guidelines 2010 are published so that consistency

This article is based on the studies first reported in the JPN guidelines for the management of acute pancreatitis. 3rd ed. JPN Guidelines 2010 (in Japanese). Tokyo: Kanehara; 2009.

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between the criteria for severity assessment in the first edition and the new criteria will be maintained. In the new criteria, severity assessment can be made only by calculating the 9 scored prognostic factors. Severity assessment according to the contrast-enhanced computed tomography (CT) grade was made by scoring the poorly visualized pancreatic area in addition to determining the degree of extrapancreatic progress of inflammation and its extent. Changes made in accordance with the new criteria are seen in various parts of the guidelines. In the present revised edition, post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is treated as an independent item. Furthermore, clinical indicators (pancreatitis bundles) are presented to improve the quality of the management of acute pancreatitis and to increase adherence to new guidelines.

Keywords Acute pancreatitis · Gallstone-induced pancreatitis · Post-ERCP pancreatitis · Pancreatitis bundle · Guidelines

Introduction

The first edition of the JPN guidelines for the management of acute pancreatitis was published in 2006 in the journal of *Hepato-Biliary-Pancreatic Surgery* 2006; 13:2–6 [1]. Looking back at the circumstances until the publication of the present English-language version, the results of long-time endeavor by the working group for developing the JPN guidelines become apparent. The first Japanese edition of the Guidelines for the management of acute pancreatitis was published in 2003 [2].

In 1994, the Japanese Society for Abdominal Emergency Medicine organized a working group involved in the preparation of guidelines for the management of acute pancreatitis. The first Japanese edition of the Guidelines for the management of acute pancreatitis was published owing to the painstaking activities on the part of the working group, including a search for systematic evidence and the preparation of a definite statement of recommendations along with the levels of the recommendations and a flow chart. A second edition was published 4 years after the publication of the first edition. During the 4 years after the publication of the first edition in 2003, the mortality rate of acute pancreatitis in Japan was reduced from 7.2 to 2.9%, although it exceeded 30% in the most severe cases. Under these circumstances, aid for medical expenses is provided for specified intractable diseases in Japan.

Doubts will be cast as to the reason for publishing a revised edition of the Guidelines for the management of acute pancreatitis: the JPN guidelines 2010, at this time. The rationale for this is that new criteria for the severity assessment of acute pancreatitis were made public on the basis of activities and reports of shared studies that were conducted in 2008. The new severity classification is entirely different from that adopted in the 2006 guidelines. A drastic revision was made in the new criteria. For example, about half of the cases that have been assessed previously as being 'severe' are assessed as being 'mild' in the new criteria. The JPN guidelines 2010 are published so that consistency between the criteria for severity assessment in the first edition and the new criteria will be maintained. In the present new criteria, severity assessment can be made only by calculating the 9 scored prognostic factors. Severity assessment according to the contrast-enhanced CT grade was made by scoring the poorly visualized pancreatic area in addition to determining the degree of extrapancreatic progress of inflammation and its extent. Revisions made in accordance with the new criteria are seen in various parts of the guidelines. In the present revised edition, post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is treated as an independent item. Furthermore, clinical indicators (pancreatitis bundles) are presented to improve the quality of management of acute pancreatitis and increase adherence to guidelines.

The Japanese Society for Abdominal Emergency Medicine, the Japan Pancreas Society, the Research Group (Ministry of Health, Labour, and Welfare) for Intractable Diseases and Refractory Pancreatic Diseases (under the sponsorship of the Japanese Ministry of Health, Labour, and Welfare), the Japanese Radiological Society, and the Japanese Society of Hepato-Biliary-Pancreatic Surgery were commissioned to produce the JPN Guidelines for the management of acute pancreatitis.

The overall contents of the JPN Guidelines 2010 for the management of acute pancreatitis

The JPN Guidelines 2010 for the management of acute pancreatitis, to be published in the Journal of Hepato-Biliary-Pancreatic Sciences (J Hepatobiliary Pancreat Sci 2010; 1) are divided into the following 11 topics.

1. Tadahiro Takada, et al. Cutting-edge information for the management of acute pancreatitis: JPN Guidelines 2010
2. Masahiro Yoshida et al. Health insurance and payment systems for severe acute pancreatitis: JPN Guidelines 2010

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The Universal Medical Care Insurance system, which is a unique health insurance system of Japan, is described.

3. Miho Sekimoto, et al. National survey of effect of clinical practice guidelines for acute pancreatitis: JPN Guidelines 2010
   Changes in the management of acute pancreatitis after the publication of the first edition of the JPN Guidelines are presented mainly on the basis of the results of questionnaire research.
4. Seiki Kiriyama, et al. New diagnostic criteria of acute pancreatitis: JPN Guidelines 2010
   In making a diagnosis of acute pancreatitis, reference is often made to cut-off values of serum pancreatic enzymes, such as a level that is elevated by more than 3 times the normal range. However, due to the lack of definite evidence of the relevance of these values, discussion of these cut-off values was excluded. Furthermore, the diagnostic shortcomings of an elevated level of serum amylase are referred to, and the reason for inclusion of the significance of serum lipase tests is presented.
5. Kazunori Takeda, et al. Assessment of severity of acute pancreatitis according to new prognostic factors and CT grading: JPN Guidelines 2010
   Severity assessment made according to the scored prognostic factors and the contrast-enhanced CT grading is discussed. The severity assessment made according to two methods is described by comparison with the old severity scoring used in the first edition. For those cases that have been assessed as being severe according to the prognostic factors of either of the two methods, the mortality rate can be calculated more clearly when severity assessment is made by combination with the contrast-enhanced CT grade.
6. Morihisa Hirota, et al. Fundamental and intensive care of acute pancreatitis: JPN Guidelines 2010
   Description is focused on the basic treatment policy for acute pancreatitis (fluid replacement, nasogastric tube, nutrition, antibiotics, and protease inhibitors. Also described as special treatment are selective decontamination of the digestive tract (SDD), continuous hemodiafiltration (CHDF), continuous regional arterial infusion of protease inhibitors, and the use of antibiotics.
7. Hodaka Amano, et al. Therapeutic intervention and surgery for acute pancreatitis: JPN Guidelines 2010
   Changes in operative indications for acute pancreatitis, necrotizing pancreatitis, and infected pancreatitis are discussed in particular.
8. Yasutoshi Kimura, et al. Gallstone-induced acute pancreatitis: JPN Guidelines 2010
   Description is focused on the algorithm of gallstone-induced pancreatitis.
9. Shinju Arata, et al. Post-ERCP pancreatitis: JPN Guidelines 2010
   Assessment of post-ERCP pancreatitis as an independent item; its epidemiology, risk factors, and diagnosis are described.
10. Keita Wada, et al. Strategy for the management of acute pancreatitis: JPN Guidelines 2010
    By means of a flow chart, explanation is given that shows how to cope with patients in whom acute pancreatitis is suspected or those with a definitive diagnosis of acute pancreatitis. The flow chart for the management of gallstone-induced pancreatitis is presented independently.
11. Toshihiko Mayumi, et al. Pancreatitis bundles: JPN Guidelines 2010
    Current characteristics of other bundles and pancreatitis bundles are presented.

Categories of evidence and the grading of recommendations

The evidence obtained from each reference item was evaluated in accordance with the method of scientific classification used at the Cochrane Library (March, 2009) (Table 1) [1–3], and the quality of evidence for each parameter associated with the diagnosis and treatment of acute pancreatitis was determined. The relevant terms used are explained in the footnote of Table 1 [13]. Based on the results obtained from these procedures, recommendation grades of A–D were determined according to the definitions shown in Table 2, and the recommendation grades are mentioned, as required, in the text of the Guidelines. The grading is based on the classification of the modified Tokyo guidelines [4].

Recommendations graded as either A or B indicate high quality. Grade C1 shows that the use of the procedures may be considered, although there is only a small amount of scientific evidence for them. On the other hand, Grade C2 shows that the use of the procedures cannot be definitely recommended due to lack of a sufficient amount of scientific evidence. Procedures graded as D are considered to be unacceptable. It must be borne in mind that such recommendation grades merely represent standards and should not be used to compel adherence to a given method of medical management in an actual clinical setting. The medical management method that is applied should be selected after taking into account the conditions prevailing at the relevant institution (e.g., staff, experience, and equipment) and the characteristics of the individual patient.

Table 1 Treatment/prevention and cause/harm

Level	Therapy/prevention, etiology/harm	Prognosis	Diagnosis	Differential diagnosis/ symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity[a]) of RCTs	SR (with homogeneity[a]) of inception cohort studies; CDR[b] validated in different populations	SR (with homogeneity[a]) of level 1 diagnostic studies; CDR[b] with 1b studies from different clinical centers	SR (with homogeneity[a]) of prospective cohort studies	SR (with homogeneity[a]) of level 1 economic studies
1b	Individual RCT (with narrow confidence interval[c])	Individual inception cohort study with >80% follow-up; CDR[b] validated in a single population	Validating[k] cohort study with good[j] reference standards; or CDR[b] tested within one clinical center	Prospective cohort study with good follow-up[m]	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none[d]	All or none case-series	Absolute SpPins and SnNouts[g]	All or none case-series	Absolute better-value or worse-value[h] analyses[j]
2a	SR (with homogeneity[a]) of cohort studies	SR (with homogeneity[a]) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity[a]) of level >2 diagnostic studies	SR (with homogeneity[a]) of 2b and better studies	SR (with homogeneity[a]) of level >2 economic studies
2b	Individual cohort study (including low-quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow up of untreated control patients in an RCT; Derivation of CDR[b] or validated on split-sample[f] only	Exploratory[k] cohort study with good[j] reference standards; CDR[b] after derivation, or validated only on split-sample[f] or databases	Retrospective cohort study, or poor follow up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity[a]) of case–control studies		SR (with homogeneity[a]) of 3b and better studies	SR (with homogeneity[a]) of 3b and better studies	SR (with homogeneity[a]) of 3b and better studies
3b	Individual case–control study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case-series (and poor quality cohort and case–control studies[e])	Case-series (and poor quality prognostic cohort studies[l])	Case–control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis

Table 1 continued

Level	Therapy/prevention, etiology/harm	Prognosis	Diagnosis	Differential diagnosis/ symptom prevalence study	Economic and decision analyses
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

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Users can add a minus-sign "−" to denote the level of a study that fails to provide a conclusive answer because there is

EITHER a single result with a wide confidence interval OR a systematic review with troublesome heterogeneity

Such evidence is inconclusive, and therefore can only generate Grade D recommendations

[a] By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "−" at the end of their designated level

[b] Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)

[c] See note above for advice on how to understand, rate, and use trials or other studies with wide confidence intervals

[d] Met when all patients died before the treatment (Rx) became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it

[e] By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow up of patients. By poor quality case–control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders

[f] Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples

[g] An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis

[h] Good, better, bad, and worse refer to the comparisons between treatments in terms of their clinical risks and benefits

[i] Good reference standards are independent of the test, and are applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study

[j] Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and equally or more expensive

[k] Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'

[l] By poor quality prognostic cohort study we mean one in which sampling was biased in favor of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors

[m] Good follow up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example, 1–6 months acute; 1–5 years chronic)

Table 2 Grades of recommendation

Grade of recommendation	Contents
A	Recommended strongly to perform Evidence is strong and clear clinical effectiveness can be expected
B	Recommended to perform Evidence is moderate or strong, although evidence of effectiveness is sparse
C1	Evidence is sparse, but may be considered to perform Effectiveness can possibly be expected
C2	Scientific evidence is not sufficient, so clear recommendation cannot be made Evidence is not sufficient to support or deny effectiveness
D	Considered to be unacceptable There is evidence to deny effectiveness (to show harm)

The Minds Manual for Preparation of Management Guidelines [2007 edition] (included as a reference after translation into English) cited with modifications from the Tokyo Guidelines [4]

The quality of evidence in each item related to the diagnosis of acute pancreatitis was determined on the basis of the assessment of evidence introduced in each reference according to the evidence-based classification adopted in the Cochrane library (Oxford Centre for Evidence-based Medicine and Levels of Evidence) (March, 2009) [1–3]. The levels of evidence in all the references cited in the present Guidelines are shown in parentheses at the end of each reference in the reference list.

The grades of recommendation were determined and included as appropriate in the present guidelines by considering medical circumstances in Japan (characteristics of medical practice and the insurance system) and in reference to the level of evidence obtained from each reference and the grades of recommendation shown in Table 2. In making use of the grades of recommendation in actual situations, consider the notes that are included as appropriate.

Note that the above recommendations are the most standardized criteria, but that the present guidelines have no intention of compelling the use of the recommendations in actual medical practice. The final decision should be made after having taken into consideration the condition of facilities (e.g., personnel, experience, and equipment)and circumstances that individual patients are placed in.

Procedures can be rated as Grade A or B, in which performance is recommended. On the contrary, the performance of procedures rated as Grade D is not recommended. As for Grade C, Grade C1 suggests that effectiveness can be expected although there is only a small amount of scientific evidence, while Grade C2 suggests that there is an insufficient amount of scientific evidence to support or deny effectiveness.

Notes on the use of the guidelines

The Guidelines are evidence-based and determined with a grade for each medical practice, taking actual conditions into account. The Guidelines specify the criteria for the diagnosis of acute pancreatitis and the assessment of its severity that have been prepared by the Research Group and are in widespread use in Japan. Because the Guidelines address so many different topics, an index of all works used is included at the end of the Guidelines. Dosages described in the text of the guidelines are for adult patients.

Definition of terminology

A certain degree of consensus has been obtained to date concerning the definition of acute pancreatitis and its complications, in reference to the guidelines of international conferences in Marseilles (1963) [5], Cambridge (1983) [6], Marseilles (1984) [7], Marseilles-Rome (1988) [8], and Atlanta (1992) [9], as well as the guidelines of the Intractable Pancreatic Disease Investigation and the Research Group of the Japanese Ministry of Health, and Welfare (1987) [10] and those of the British Society of Gastroenterology 1998) [11]. However, there remain many ambiguous elements in the definitions of terminology associated with acute pancreatitis, so new terminology is proposed below.

Acute pancreatitis

Acute pancreatitis is defined as an inflammation that has occurred in the pancreas and that can affect remote organs as well as the adjacent organs. It was decided that acute exacerbation of chronic pancreatitis should be dealt with in separate items according to the causes that give rise to acute pancreatitis (such as acute alcoholic pancreatitis and gallstone-induced pancreatitis).

Clinical features of acute pancreatitis

In most cases, acute pancreatitis occurs suddenly and is accompanied by upper abdominal pain and various types of