Bijlagen bij de conceptrichtlijn Acute Pancreatitis

INITIATIEF
Nederlandse Vereniging van Maag-Darm-Leverartsen (NVMDL)

IN SAMENWERKING MET
Nederlandse Vereniging voor Heelkunde (NVvH)
Nederlandse Vereniging voor Radiologie (NVvR)
Nederlandse Vereniging voor Intensive Care (NVIC)
Nederlandse Vereniging van Diëtisten (NVD)
Nederlandse Vereniging voor Medische Microbiologie (NVMM)
Nederlandse Vereniging voor Anesthesiologie (NVA)
Nederlandse Internisten Vereniging (NIV)
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Colofon

CONCEPTRICHTLIJN ACUTE PANCREATITIS

Nederlandse Vereniging van Maag-Darm-Leverartsen
Wilhelminastraat 13 ZW
2011 VH HAARLEM
023-5513016
secretariaat@mdl.nl
www.mdl.nl

Inhoudsopgave

Dit document bevat de achtergrondinformatie behorende bij de moduleteksten van de richtlijn Acute Pancreatitis. Het staat u vrij om commentaar op deze bijlagen te geven; dit is niet noodzakelijk.

Bijlage 1. Verantwoording

Voor meer details over de gebruikte richtlijnmethodologie verwijzen wij u naar de Werkwijze. Relevante informatie voor de ontwikkeling/herziening van deze richtlijnmodule is hieronder weergegeven.

Algemene gegevens

De ontwikkeling/herziening van deze richtlijnmodule werd ondersteund door het Kennisinstituut van de Federatie Medisch Specialisten (www.demedischspecialist.nl/kennisinstituut) en werd gefinancierd door de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS). De financier heeft geen enkele invloed gehad op de inhoud van de richtlijnmodule.

Samenstelling werkgroep

Voor het ontwikkelen van de richtlijn is in 2023 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen (zie hiervoor de Samenstelling van de werkgroep) die betrokken zijn bij de zorg voor volwassen patiënten met (een vermoeden op) acute pancreatitis.

Belangenverklaringen

Een overzicht van de belangen van werkgroepleden en klankbordgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabellen. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten via secretariaat@kennisinstituut.nl.

Tabel 1 Gemelde (neven)functies en belangen werkgroep

Naam	Hoofdfunctie	Nevenwerkzaamheden	Persoonlijke financiële belangen	Persoonlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Dr. R.C. Verdonk (voorzitter)	MOL-arts In het st. Antonius ziekenhuis. Werkzaam binnen vrijgevestigd maatschapsverband van de maatschap inwendige ziekten.	"Voorzitter Regionaal Expert-team HPB oncologie - Bestuurslid Pancreatitis Werkgroep Nedelrand (PWN) - Lid MEC-U (Supra-regionale METc) - Lid van diverse DSMB's en studie-protocol commissies - Lid werkgroep aanpassing module richlllijn galsteenlijden NWH - Lid Denktank Deltplan alvleesklierkanker - Lid werkgroep kennisagenda MDL van de NVMDL - Lid van diverse wetenschappelijke verenigingen	Geen	Geen	"1. ZonMW - COBRA studie, cholangltis behandeling (Projectleider NEE) 2. ZonMW - RACCOON studie, RFA bij cholagiocarcinoom (Projectleider NEE) 3. ZonMW - PEARL studie, rlfaximin na TIPS plaatsing (Projectleider NEE) 4. ZonMW - PIANO studie, behandeling geinfecteerde pancreasnecrose (Projectleider NEE) 5. Boston Scientific Axioma studie,	Geen	Geen	20-09-2023	Geen

		Geen van de functies is betaald, muv van de METC. Hiervoor worden vacatie-gelden uitgekeerd aan de maatschap inwendige ziekten St. Antonius Ziekenhuis"			gebruik Ho!Axios bij pancreascollecti es (Projectleider NEE)"				
Dr. K. Boonstra	Maag-, darm- en leverarts Radboud umc	Geen	Geen	Geen	Lokaal onderzoeker voor industry initiated onderzoek Mirum Pharma 1. Mirum Pharma - local investigator VISTAS study, volixibat for cholestatic itch PSC (Projectleider NEE) 2.Mirum Pharma - local investigator VANTAGE study, volixibat for cholestatic itch PBC (Projectleider NEE)	Geen intellectueel belang of reputatie.	Geen	14-01-2025	Geen
Dr. W.J. Lammers	MDL-arts Erasmus MC	Geen	Geen	Geen	Participatie in studies acute pancreatitis (zie hieronder) als lokale PI. 1. Interscope, endorotor, necrotiserende pancreatitis. 2. Dr. rer. nat. Valentin Faerber, Director / medical Science and IITs, omega-3 vetzuren bij patienten met voorspeld ernstige pancreatitis	contactpersoon EMC landelijke pancreatitis patientenorgani satie	Geen	3-02-2024	Geen
Dr. R.P. Voermans	MDL-arts Amsterdam UMC	Geen	Geen	Geen	Geen	Geen	Geen	4-12-2024	1. Neerlegg en adviesrad en gedurend e richtlijno ntwikkeli ngstrajec t (besluit van werkgroe plid om

									advies niet op te volgen). 2. Restrictie m.b.t. besluitvorming over de plaats van galwegstents bij pancreascollecties.
Prof. Dr. M. Besselink	Hoogleraar chirurgie Amsterdam UMC	Geen	Geen	Geen	Uitsluitend investigator initiated onderzoek. Intuitive Surgical: DIPLOMA 2x2 trial: RCT robot vs open Whipple Ethicon: PANDORINA trial: RCT wel/geen drain na pancreasstaart resectie, projectleider. Oncosil: PANCOSIL trial: fase single arm trial percutane applicatie Oncosil bij lokaal gevorderd pracreascarcinoom, projectleider.	Geen	Geen	4-3-2025	Restricties ten aanzien van besluitvorming betreffende de behandeling met OM-3 FA's bij patienten met voorspeld ernstige pancreatitis. Overige onderwerpen van commercieel gefinancieerd onderzoek valt buiten bestek van richtlijn.
Dr. S.A.W. Bouwense	chirurg, MUMC+. fulltime, betaald	Geen	Geen	Geen	Onderzoeker PLANCTON studie voor de Pancreatitis Werkgroep Nederland: visolie of normale behandeling in vroege fase van pancreatitis. Ondersteuning door Fresenius Kabi voor deze studie. Investigator-initiated trial. 1. Fresenius Kabi - LANCTON studie voor de Pancreatitis Werkgroep Nederland:	Geen	Geen	8-01-2025	Restricties ten aanzien van besluitvorming betreffende de behandeling met OM-3 FA's bij patienten met voorspeld ernstige pancreatitis. Andere onderwerp van commerc

					visolie of normale behandeling in vroege fase				ieel gefinanci eerd onderzoe k valt buiten bestek van richtlijn.
Dr. T.L. Bollen	Radioloog St Antonius Ziekenhuis Nieuweg ein/Utrec ht	Geen	Geen	Geen	Geen	Geen	Geen	4-12-2024	Geen
M.A. Vis (tot juni 2026)	Voorzitte r Alvleeskli erverenig ing Nederlan d	Geen	Geen	Pwn	Geen	Geen	Geen	6-2-2025	Geen

Tabel 2 Gemelde (neven)functies en belangen klankbordgroep

Naam	Hoofdfun ctie	Nevenwerkzaamhed en	Persoonli jke financiël e belangen	Persoo nlijke relaties	Extern gefinancierd onderzoek	Intellectuele belangen en reputatie	Overige belangen	Datum	Restrictie
Dr. M. Smit	chirurg-intensivis t Intensive Care Volwasse nen Universit air Medisch Centrum Groninge n Betaalde functie Werkzaa m in kliniek, op het gebied van onderwijs , research en managem ent	Geen	Geen	Geen	2022-2025 Samenwerking met Potrero Medical (latere naam: Accuryn Medical) waarbij dit bedrijf Accuryn Monitoring Devices in bruikleen gaf en disposable urinecatheters leverde voor diverse onderzoeken. Bij deze onderzoeken werden buikdrukken geautomatiseer d gemeten en de urineproductie geautomatiseer d bijgehouden. Er zijn geen betalingen	Geen	Geen	17-1-2025	Geen restrictie s (onderwe rp van commerc ieel gefinanci erd onderzoe k valt buiten bestek van richtlijn).

					geweest van het bedrijf aan de onderzoekers. 1. Potrero Medical - Buikdruk metingen in cardiochirurgische patienten (Projectleider JA) 2. Potrero Medical - Buikdrukmetingen en urineproductie in levertransplantatie patienten (Projectleider JA) 3. Accuryn Medical - Buikdrukmetingen in laparoscopieen (Projectleider JA)				
K. Mertens	Diëtist bij Bravis Ziekenhuis	Lid MDL diëtisten netwerk en diëtisten netwerk coeliakie (beide onbetaald)	geen	geen	geen	Unieke expertise op het gebied van voeding bij acute pancreatitis	geen	16-4-2025	Geen
Dr. E. Sieswerda	Arts-microbioloog Werkgever: UMC Utrecht (tot 30 april 2025); ECRAID (per 1 mei 2025)	Coordinator SWAB sepsis richtlijn update	geen	geen	1. ZonMW - Antibiotic stewardship bij acute pancreatitis (PIANO trial) (Projectleider JA) 2. ABR zorgnetwerk Utrecht - Verbeteren antibioticagebruik urineweginfecties kwetsbare ouderen (Projectleider JA) 3.ZonMW - Behandelduur cholangitis (COBRA trial) (Projectleider NEE) 4.EU Horizon 2020 - Huid- op huidcontact ter preventie van neonatale sepsis en	geen	geen	16-4-2025	Geen

					resisten kolonisatie (NeoDeco/NeoIPC) (Projectleider NEE) 5.ZonMW -=Reinfecties na sepsis op de IC (Mars.url) (Projectleider NEE)				
Dr. Raha Nabbi	Anesthesioloog pijnspecialist in het UMCG	geen	geen	geen	geen	geen	geen	28-5-2025	Geen
Dr. M. van Bemmel	Internist, Fundashon Mariadal Bonaire	geen	geen	geen	geen	geen	geen	24-1-2025	Geen

Inbreng patiëntenperspectief

De werkgroep besteedde aandacht aan het patiëntenperspectief door een afgevaardigde van de patiëntenorganisatie Alvleeskliervereniging Nederland. De conceptrichtlijn is tevens voor commentaar voorgelegd aan de Alvleeskliervereniging Nederland en de eventueel aangeleverde commentaren zijn bekeken en verwerkt.

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz

Bij de richtlijnmodule voerde de werkgroep conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uit om te beoordelen of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling is de richtlijnmodule op verschillende domeinen getoetst (zie het stroomschema bij Werkwijze).

Module	Uitkomst raming	Toelichting
Module 1. Diagnostiek eerste episode acute pancreatitis	Geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module 2. Voorspellen van de ernst van acute pancreatitis	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet. Er worden daarom geen substantiële financiële gevolgen verwacht.
Module 3. Vullingsbeleid bij acute pancreatitis	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet. Er worden daarom geen substantiële financiële gevolgen verwacht.
Module 4. Voedingsbeleid bij acute pancreatitis	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm voldoet. Er worden daarom geen substantiële financiële gevolgen verwacht.
Module 5. Pijnbehandeling bij acute pancreatitis	Geen financiële gevolgen	Hoewel uit de toetsing volgt dat de aanbeveling(en) breed toepasbaar zijn (5.000-40.000 patiënten), volgt ook uit de toetsing dat het overgrote deel (±90%) van de zorgaanbieders en zorgverleners al aan de norm

		voldoet. Er worden daarom geen substantiële financiële gevolgen verwacht.
Module 6. Antibiotica bij verdenking geïnfecteerde necrotiserende pancreatitis	Geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module 7. Optimale timing van initiële drainage bij geïnfecteerde necrotiserende pancreatitis	Geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.
Module 8. Aanvullende necrosectomie bij geïnfecteerde necrotiserende pancreatitis	Geen financiële gevolgen	Uit de toetsing volgt dat de aanbeveling niet breed toepasbaar zijn (<5.000 patiënten) en daarom naar verwachting geen substantiële financiële gevolgen zal hebben voor de collectieve uitgaven.

Module 1. Diagnostiek bij een eerste episode acute pancreatitis

Introduction (English)

During a first episode of acute pancreatitis, adults aged 30–70 are most commonly affected. The primary causes are gallstones and alcohol use. Diagnosis is based on clinical presentation, elevated amylase or lipase levels, and/or imaging—typically abdominal ultrasound, sometimes followed by a CT-scan. Management generally involves hospital admission, fluid resuscitation, pain control, and assessing and, if possible, treating the underlying cause, such as gallstones. Current challenges include delays in identifying the etiology, inconsistent diagnostic approaches, and variation in consultations and follow-up care. These inefficiencies may result in prolonged hospital stays, complications, or recurrent acute pancreatitis. Timely and accurate diagnostics, early targeted treatment, and structured aftercare could significantly improve clinical outcomes. Such improvements would reduce complications, shorten hospital stays, and lower recurrence rates.

Search and select

A systematic review of the literature was performed to answer the following questions:

1. What are the (un)beneficial effects of adding EUS to standard diagnostic trajectory in adults (≥18 years) presenting with a first episode of suspected idiopathic acute pancreatitis, compared to not adding a test to standard diagnostic trajectory?

2. What are the (un)beneficial effects of adding MRI/MRCP to standard diagnostic trajectory in adults (≥18 years) presenting with a first episode of suspected idiopathic acute pancreatitis, compared to not adding a test to standard diagnostic trajectory?

Table 1. PIC(R)O

Patients	Adults (≥18 years) presenting with a first episode of suspected idiopathic acute pancreatitis in an emergency or hospital setting following standard diagnostic trajectory (blood test*, anamnesis and abdominal ultrasound <48 hours**) * calcium, albumin, triglyceride **used to identify gallstones or biliary etiology as the cause of acute pancreatitis
Index test	1.EUS 2.MRI/MRCP scan Both: during admission, ultimately <4 weeks
Comparator test	No additional test
Reference test	NA
Outcomes	Recurrence acute pancreatitis, detection of etiology, quality of life
Other selection criteria	Study design: systematic reviews, randomized controlled trials and observational studies. Search from 2015.

<u>Relevant outcome measures</u>

The guideline panel considered recurrence of acute pancreatitis as a **critical** outcome measure for decision making; and detection of etiology and quality of life as **important** outcome measures for decision making.

The guideline panel defined the outcome measures as follows:

- Recurrence acute pancreatitis, defined as two or more distinct episodes of acute pancreatitis, with complete or near-complete resolution of symptoms and pancreatic inflammation between episodes, and without evidence of chronic pancreatitis
- Detection of etiology, defined as the identification of a specific underlying cause of acute pancreatitis through diagnostic evaluation that explains the pancreatitis episode and was not previously identified during the initial standard diagnostic workup
- Quality of life, defined as patient-reported health status measured using validated health-related quality-of-life questionnaires.

The guideline panel defined the following thresholds for minimal clinically important differences:

- Mortality: a relative risk of ≤ 0.91 or ≥ 1.10;
- Other dichotomous outcome measures: a relative risk of ≤ 0.80 or ≥ 1.25;
- Continuous outcome measures: 0.5 x median baseline standard deviation (SD) or 0.5 x standardized mean difference (SMD).

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2015 to the 16th of September 2025 for systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from four primary search concepts: (1) acute pancreatitis; (2) etiology; (3) endoscopic ultrasonography; (4) MRI/MRCP. Duplicates were removed using EndNote software. After deduplication and removing of retracted articles a total of 882 records were imported for title/abstract screening. Initially, 4 studies were selected based on title and abstract screening. After reading the full text, these studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and as a result no studies could be included in the literature analysis.

Summary of literature

The search resulted in four potentially relevant studies. Full-text assessment led to exclusion of all four studies (see exclusion table), leaving no studies that met the criteria for inclusion in the systematic literature analysis.

Description of studies

N.A.

Results

N.A.

Summary of Findings

N.A.

Kennisvragen

Tijdens de ontwikkeling van deze module is systematisch naar onderzoeken gezocht die de zoekvraag kunnen beantwoorden. Door gebruik te maken van een systematische literatuuranalyse met beoordeling van de bewijskracht is duidelijk geworden dat er binnen deze module nog kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvragen:

1. Wat is de toegevoegde waarde van MRI/MCRP op aanvullende EUS bij negatieve work-up voor etiologie van acute pancreatitis?
   P: Patiënten met een eerste episode van idiopathische acute pancreatitis en een negatieve standaard diagnostische work-up
   I: toevoegen van MRI/MRCP aan EUS
   C: EUS alleen
   O: diagnostische opbrengst voor behandelbare oorzaken van acute pancreatitis
2. Welke patiëntkenmerken of subgroepen voorspellen dat aanvullende diagnostiek met EUS of MRI/MRCP een behandelbare etiologie aantoont bij een eerste episode van idiopathische acute pancreatitis?
   P: Patiënten met een eerste episode van idiopathische acute pancreatitis en een negatieve standaard diagnostische work-up
   I: patiënt-, ziekte- of beeldvormingskenmerken
   C: patiënten zonder deze kenmerken
   O: detectie van een behandelbare etiologie door EUS en/of MRI/MRCP
3. Wat zijn de kosteneffectiviteit en de impact op zorggebruik (aantal onderzoeken, ziekenhuisopnames en behandelingen) van het toevoegen van EUS en/of MRI/MRCP aan de standaard diagnostische work-up bij deze patiëntengroep?
   P: patiënten met een eerste episode van idiopathische acute pancreatitis en een negatieve standaard diagnostische work-up
   I: kosteneffectiviteit van het toevoegen van EUS en/of MRI/MRCP
   C: standaard diagnostische work-up
   O: kosten, zorggebruik, ziekenhuisopnames, diagnostische onderzoeken en behandelingen

Toelichting:

Deze kennisvragen zijn relevant omdat er geen studies konden worden geïncludeerd die voldeden aan de vooraf opgestelde selectiecriteria, waardoor onzeker blijft of toevoeging van EUS en/of MRI/MRCP aan de standaard diagnostische work-up daadwerkelijk leidt tot betere klinische uitkomsten, zoals minder recidieven, minder complicaties of betere kwaliteit van leven. Daarnaast is onduidelijk wat de plaats van MRI/MRCP is ten opzichte van EUS, met name wanneer EUS geen etiologie aantoont of wanneer MRI/MRCP als aanvullend of alternatief onderzoek wordt overwogen. Ook is meer inzicht nodig in welke patiëntkenmerken of subgroepen de grootste kans hebben op het aantonen van een behandelbare etiologie, zodat aanvullende diagnostiek gerichter kan worden ingezet. Toekomstig onderzoek zou bij voorkeur prospectief en multicentrisch moeten zijn, met vergelijking van diagnostische strategieën, registratie van klinische uitkomsten en een economische evaluatie waarin kosten, zorggebruik en mogelijke besparing door voorkomen recidieven worden meegenomen.

Implementeren-tabel

Vraag	*Antwoord: Kruis aan en licht toe/ beschrijf*		*Toelichting keuze:*
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X**	Ongewenste praktijkvariatie	Er bestaat ongewenste praktijkvariatie in de diagnostiek na IAP: EUS wordt niet overal routinematig of op hetzelfde moment ingezet, terwijl dit bepalend kan zijn voor vervolgbeleid (bijv. cholecystectomie, oncologische verwijzing of vervolgbeeldvorming).
	X	Nieuwe evidentie	De PICUS-studie (2023) liet bij een eerste IAP-episode een diagnostische opbrengst van 32% zien wanneer EUS werd toegevoegd.
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**X**	< 1000 - maximaal enkele honderden patiënten per jaar. Het gaat niet om alle patiënten met acute pancreatitis, maar de subgroep met idiopathische acute pancreatitis na initiële standaard workup.	
		< 5000	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?	**X**	Ja	Deze module is verwant aan andere modules binnen de richtlijn 'acute pancreatitis' en verwant aan de internationale richtlijn acute pancreatitis (PMID: 40651900).
		Nee	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**

Richtlijn/ klinisch traject (innovatie)		Afwezigheid van een lokaal zorgpad.	Sterke internationale aanbeveling en Nederlandse PICUS-studie ondersteunen uniformering. In te bouwen in de pancreatitis-zorgpaden in lokale ziekenhuizen.
Zorgverleners (artsen en verpleegkundigen)		Verschillende voorkeuren tussen specialismes en beperkte bekendheid met de opbrengst van EUS bij een eerste episode van idiopathische acute pancreatitis. Verschil in ervaring van endosonografist.	Multidisciplinaire afspraken, nascholing, standaard verwijscriteria.
Patiënt/ cliënt (naasten)		EUS is invasief, vereist sedatie en een extra afspraak; patiënten kunnen voorkeur hebben voor een MRI/MRCP of angst ervaren.	Heldere patiëntinformatie over het doel, belasting, risico's en mogelijke behandelbare oorzaken. Vervolgafspraken al voor ontslag inplannen.
Sociale context		Reisafstand, werk/gezinsbelasting, taalbarrieres en sociale milieu kunnen leiden tot no-show of vertraging.	Betrek naasten, geef begrijpelijke schriftelijke/digitale informatie en organiseer regionale toegang tot EUS door verwijsafspraken.
Organisatorische context		Niet ieder ziekenhuis heeft de beschikking over EUS. Wachttijden kunnen oplopen. Er is afstemming nodig tussen verwijzende ziekenhuizen en EUS-centra.	Regionale afspraken. Ontslagplanning met afspraak voor ontslag uit het ziekenhuis.
Financiële en juridische context		Financiering kan los staan van de indexopname met acute pancreatitis.	Vroeg opsporen van etiologie kan recidieven en heropnames voorkomen. Onderbouwing door richtlijn en PICUS-trial vergemakkelijkt het

			maken van contracten en financiering.
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** ***Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.***		**A**	**B**
		Patiënt/ cliënt (naaste)	informeren over reden voor EUS, belasting en alternatieven; verschijnen op poliklinische afspraak; recidiefklachten, alcohol/medicatie, familieanamnese en voorkeuren bespreken.
		Professional	MDL-artsen passen het zorgpad toe, vragen EUS tijdig aan, bewaken uitslagen en regelen vervolgbeleid
		Beroepsvereniging, nl	kunnen scholing, standaardteksten, verwijscriteria en indicatoren faciliteren
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	borgen van lokale protocollen, EUS-capaciteit of regionale verwijsafspraken, planning vóór ontslag, EPD-ondersteuning en periodieke audit/terugkoppeling.
		Zorgverzekeraars/ NZa	zo nodig faciliteren van passende bekostiging en contractering van regionale EUS-capaciteit, vooral voor ziekenhuizen zonder eigen EUS-functie
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	**< 1 jaar**	Haalbaar voor centra met voldoende EUS-capaciteit en bestaand pancreatitis-zorgpad; brede landelijke invoering vraagt meer afstemming

		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? ***De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.***	**X**	**Ja**	Publicatie alleen is waarschijnlijk onvoldoende voor uniforme toepassing. Nodig zijn: lokaal/regionaal zorgpad, afspraken over EUS-toegang en wachttijd, ontslagchecklist, patienteninformatie, scholing en auditindicatoren.
		Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. ***Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.***		**Ja ***	
	X	**Nee**	

Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.

Literatuur

Hallensleben ND, Umans DS, Bouwense SA, Verdonk RC, Romkens TE, Witteman BJ, Schwartz MP, Spanier MB, Laheij R, van Santvoort HC, Besselink MG, van Hooft JE, Bruno MJ; Dutch Pancreatitis Study Group. The diagnostic work-up and outcomes of 'presumed' idiopathic acute pancreatitis: A post-hoc analysis of a multicentre observational cohort. United European Gastroenterol J. 2020 Apr;8(3):340-350. doi: 10.1177/2050640619890462. Epub 2019 Nov 14. PMID: 32213015; PMCID: PMC7184667.

IAP/APA/EPC/IPC/JPS Working Group. Electronic address: info@internationalpancreatology.org; IAP/APA/EPC/IPC/JPS Working Group. International Association of Pancreatology Revised Guidelines on Acute Pancreatitis 2025: Supported and Endorsed by the American Pancreatic Association, European Pancreatic Club, Indian Pancreas Club, and Japan Pancreas Society. Pancreatology. 2025 Sep;25(6):770-814. doi: 10.1016/j.pan.2025.04.020. Epub 2025 Jul 10. PMID: 40651900.

Umans DS, Timmerhuis HC, Anten MGF, Bhalla A, Bijlsma RA, Boxhoorn L, Brink MA, Bruno MJ, Curvers WL, van Eijck BC, Erkelens GW, van Geenen EJM, Hazen WL, Hoge CV, Hol L, Inderson A, Kager LM, Kuiken SD, Perk LE, Quispel R, Römkens TEH, Sperna Weiland CJ, Thijssen AY, Venneman NG, Verdonk RC, van Wanrooij RLJ, Witteman BJ, Besselink MG, van Hooft JE. Prospective multicentre study of indications for surgery in patients with idiopathic acute pancreatitis following endoscopic ultrasonography (PICUS). Br J Surg. 2023 Nov 9;110(12):1877-1882. doi: 10.1093/bjs/znad318. PMID: 37811814; PMCID: PMC10638543.

Valverde-López F, Ortega-Suazo EJ, Wilcox CM, Fernandez-Cano MC, Martínez-Cara JG, Redondo-Cerezo E. Endoscopic ultrasound as a diagnostic and predictive tool in idiopathic acute pancreatitis. Ann Gastroenterol. 2020 May-Jun;33(3):305-312. doi: 10.20524/aog.2020.0464. Epub 2020 Mar 14. PMID: 32382235; PMCID: PMC7196619.

Wilcox CM, Seay T, Kim H, Varadarajulu S. Prospective Endoscopic Ultrasound-Based Approach to the Evaluation of Idiopathic Pancreatitis: Causes, Response to Therapy, and Long-term Outcome. Am J Gastroenterol. 2016 Sep;111(9):1339-48. doi: 10.1038/ajg.2016.240. Epub 2016 Jun 21. PMID: 27325219.

Table of excluded studies

Reference	Reason for exclusion
Hallensleben ND, Umans DS, Bouwense SA, Verdonk RC, Romkens TE, Witteman BJ, Schwartz MP, Spanier MB, Laheij R, van Santvoort HC, Besselink MG, van Hooft JE, Bruno MJ; Dutch Pancreatitis Study Group. The diagnostic work-up and outcomes of 'presumed' idiopathic acute pancreatitis: A post-hoc analysis of a multicentre observational cohort. United European Gastroenterol J. 2020 Apr;8(3):340-350. doi: 10.1177/2050640619890462. Epub 2019 Nov 14. PMID: 32213015; PMCID: PMC7184667.	Wrong comparison (not compared with no additional test)
Umans DS, Timmerhuis HC, Anten MGF, Bhalla A, Bijlsma RA, Boxhoorn L, Brink MA, Bruno MJ, Curvers WL, van Eijck BC, Erkelens GW, van Geenen EJM, Hazen WL, Hoge CV, Hol L, Inderson A, Kager LM, Kuiken SD, Perk LE, Quispel R, Römkens TEH, Sperna Weiland CJ, Thijssen AY, Venneman NG, Verdonk RC, van Wanrooij RLJ, Witteman BJ, Besselink MG, van Hooft JE. Prospective multicentre study of indications for surgery in patients with idiopathic acute pancreatitis following endoscopic ultrasonography (PICUS). Br J Surg. 2023 Nov 9;110(12):1877-1882. doi: 10.1093/bjs/znad318. PMID: 37811814; PMCID: PMC10638543.	Wrong study design (no comparative study)
Valverde-López F, Ortega-Suazo EJ, Wilcox CM, Fernandez-Cano MC, Martínez-Cara JG, Redondo-Cerezo E. Endoscopic ultrasound as a diagnostic and predictive tool in idiopathic acute pancreatitis. Ann Gastroenterol. 2020 May-Jun;33(3):305-312. doi: 10.20524/aog.2020.0464. Epub 2020 Mar 14. PMID: 32382235; PMCID: PMC7196619.	Wrong comparison (first episode vs recurrent and galbladder in situ vs cholecystecomy)
Wilcox CM, Seay T, Kim H, Varadarajulu S. Prospective Endoscopic Ultrasound-Based Approach to the Evaluation of Idiopathic Pancreatitis: Causes, Response to Therapy, and Long-term Outcome. Am J Gastroenterol. 2016 Sep;111(9):1339-48. doi: 10.1038/ajg.2016.240. Epub 2016 Jun 21. PMID: 27325219.	Wrong comparison (first episode vs recurrent episodes)

5 Literature search strategy

Zoekstrategie Embase.com 16 september 2025

No.	*Query*	*Results*
#1	'pancreas necrosis'/exp OR 'acute pancreatitis'/exp OR 'acute hemorrhagic pancreatitis'/exp OR (('pancreatitis'/exp OR pancreatit*:ti,ab,kw OR ((pancrea* NEAR/3 inflammation*):ti,ab,kw)) AND ('necrosis'/de OR acut*:ti,ab,kw OR necroti*:ti,ab,kw OR necros*:ti,ab,kw)) OR 'acute pancreatit*':de	76838

#2	'etiology'/exp OR 'aetiology':ti,ab,kw OR 'emergency'/exp OR 'anamnesis'/exp OR (((unknown OR without OR unidentif* OR uncertain OR assess* OR identif* OR underly*) NEAR/3 (caus* OR orirgin)):ti,ab,kw) OR (((primary OR early OR initial OR beginning) NEAR/3 (disease* OR presentation OR symptom*)):ti,ab,kw) OR ((early NEAR/1 (predict* OR characteri* OR phase*)):ti,ab,kw) OR etiolog*:ti,ab,kw OR aetiolog*:ti,ab,kw OR idiopath*:ti,ab,kw OR 'first episod*':ti,ab,kw OR '1st episod*':ti,ab,kw OR '1 st episod*':ti,ab,kw OR 'first sign*':ti,ab,kw OR '1st sign*':ti,ab,kw OR '1 st sign*':ti,ab,kw OR unexplain*:ti,ab,kw OR cryptogenic*:ti,ab,kw OR spontaneous*:ti,ab,kw OR isolated:ti,ab,kw OR emergenc*:ti,ab,kw OR anamnes*:ti,ab,kw OR obscure*:ti,ab,kw OR onset:ti,ab,kw OR diagnosis:ti,ab,kw OR diagnosing:ti,ab,kw	9802069
#3	'endoscopic ultrasonography'/exp OR ((endoscopic* NEAR/3 (echo* OR ultraso* OR sonograph*)):ti,ab,kw) OR endosonograph*:ti,ab,kw OR eus:ti,ab,kw OR echoendoscop*:ti,ab,kw OR endoultraso*:ti,ab,kw	66683
#4	'nuclear magnetic resonance imaging'/exp OR 'mri scanner'/exp OR ('magnetic resonance':ti,ab,kw,de AND imag*:ti,ab,kw,de) OR ((magneti*:ti,ab,kw OR 'chemical shift':ti,ab,kw) AND imaging:ti,ab,kw) OR (((mr OR nmr OR 'magnetic resonance') NEAR/3 cholangiopancreatograph*):ti,ab,kw) OR mrcp:ti,ab,kw OR mri:ti,ab,kw OR mris:ti,ab,kw OR nmr:ti,ab,kw OR mra:ti,ab,kw OR mras:ti,ab,kw OR zeugmatograph*:ti,ab,kw OR 'mr tomograph*':ti,ab,kw OR 'mr imag*':ti,ab,kw OR 'proton spin*':ti,ab,kw OR fmri:ti,ab,kw OR fmris:ti,ab,kw OR rsfmri:ti,ab,kw	1842793
#5	#3 OR #4	1896593
#6	#1 AND #2 AND #5	5561
#7	#6 AND [2015-2025]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'clinical trial':dtype) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1802
#8	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR	1160886

	comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	
#9	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4903195
#10	'major clinical study'/de OR 'clinical study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR 'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR	19012278

	cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#11	#7 AND #8 - SR	104
#12	#7 AND #9 NOT #11 - RCT	224
#13	#7 AND #10 NOT (#11 OR #12) - Observationeel	498
#14	#11 OR #12 OR #13 - Totaal	826

Zoekstrategie Ovid/Medline 16 september 2025

#	Searches	Results
1	exp Pancreatitis, Acute Hemorrhagic/ or exp Pancreatitis, Acute Necrotizing/ or ((exp Pancreatitis/ or pancreatit*.ti,ab,kf. or (pancrea* adj3 inflammation*).ti,ab,kf.) and (exp Acute Disease/ or Necrosis/ or acut*.ti,ab,kf. or necroti*.ti,ab,kf. or necros*.ti,ab,kf.))	43837
2	exp Emergencies/ or ((unknown or without or unidentif* or uncertain or assess* or identif* or underly*) adj3 (caus* or orirgin)).ti,ab,kf. or ((primary or early or initial or beginning) adj3 (disease* or presentation or symptom*)).ti,ab,kf. or (early adj1 (predict* or characteri* or phase*)).ti,ab,kf. or etiolog*.ti,ab,kf. or aetiolog*.ti,ab,kf. or idiopath*.ti,ab,kf. or first episod*.ti,ab,kf. or 1st episod*.ti,ab,kf. or 1 st episod*.ti,ab,kf. or first sign*.ti,ab,kf. or 1st sign*.ti,ab,kf. or 1 st sign*.ti,ab,kf. or unexplain*.ti,ab,kf. or cryptogenic*.ti,ab,kf. or spontaneous*.ti,ab,kf. or isolated.ti,ab,kf. or emergenc*.ti,ab,kf. or anamnes*.ti,ab,kf. or obscure*.ti,ab,kf. or onset.ti,ab,kf. or diagnosis.ti,ab,kf. or diagnosing.ti,ab,kf.	5459609
3	exp magnetic resonance imaging/ or (magnetic resonance and imag*).ti,ab,kf. or ((magneti* or chemical shift) and imaging).ti,ab,kf. or ((mr or nmr or magnetic resonance) adj3 cholangiopancreatograph*).ti,ab,kf. or mrcp.ti,ab,kf. or mri.ti,ab,kf. or mris.ti,ab,kf. or nmr.ti,ab,kf. or mra.ti,ab,kf. or mras.ti,ab,kf. or zeugmatograph*.ti,ab,kf. or mr tomograph*.ti,ab,kf. or mr imag*.ti,ab,kf. or proton spin*.ti,ab,kf. or fmri.ti,ab,kf. or fmris.ti,ab,kf. or rsfmri.ti,ab,kf.	1070827
4	exp Endosonography/ or (endoscopic* adj3 (echo* or ultraso* or sonograph*)).ti,ab,kf. or endosonograph*.ti,ab,kf. or eus.ti,ab,kf. or echoendoscop*.ti,ab,kf. or endoultraso*.ti,ab,kf.	32384

5	3 or 4	1099393
6	1 and 2 and 5	1403
7	limit 6 to yr="2015 -Current"	800
8	7 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	790
9	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or (((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	861528
10	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2945606
11	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or exp cohort studies/ or epidemiologic studies/ or ((multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-	8174449

	cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/	
12	8 and 9 – SR	40
13	(8 and 10) not 12 – RCT	43
14	(8 and 11) not (12 or 13) – Observationeel	240
15	12 or 13 or 14 – Totaal	323

Module 2. Voorspellen van de ernst van acute pancreatitis

Introduction (English)

Acute pancreatitis in adults has a highly variable clinical course, ranging from mild, self-limiting disease to severe pancreatitis with organ failure and an increased risk of death. In current practice, clinicians use clinical assessment, laboratory tests, imaging and prognostic scoring systems such as APACHE II and Glasgow-Imrie to stratify risk at an early stage. Proper risk stratification is important for decisions about clinical monitoring, escalation of care and referral to expert centers. However, the timing, complexity and predictive performance of these scores differ, and it remains unclear which system provides the most useful prediction of severe disease and mortality in routine care. Identifying the score with the highest predictive value may improve early recognition of patients at risk, support more appropriate management, and ultimately contribute to better patient outcomes, including fewer preventable complications and reduced mortality. In the search, the main focus was on APACHE-II and Glasgow-Imrie, which are among the most commonly used prognostic scoring systems for acute pancreatitis in the Netherlands.

Search and select

A systematic review of the literature was performed to answer the following question(s): Which prognostic scoring system, APACHE II or Glasgow-Imrie, has the highest predictive value for severity of acute pancreatitis and mortality in adults with acute pancreatitis?

Table 1. PICOTS - Performance of prognostic instruments

Patients	Adult patients with acute pancreatitis within 48h of hospital presentation
Index instrument	Acute Physiology and Chronic Health Evaluation (APACHE) II score Predictors: 1. Body temperature (rectal, °C) 2. Mean arterial pressure (MAP), mmHg 3. Heart rate, beats per minute 4. Respiratory rate, breaths per minute 5. Oxygenation: o PaO_2 (if $FiO_2 < 0.5$), or o Alveolar-arterial (A–a) oxygen gradient (if $FiO_2 \geq 0.5$) 6. Arterial pH 7. Serum sodium, mmol/L 8. Serum potassium, mmol/L 9. Serum creatinine, mg/100 mL 10. Hematocrit, % 11. White blood cell count, total/cubic mm in 12. Glasgow Coma Scale (GCS) 13. Age, years 14. Chronic health status Predicted outcomes: - Severity of acute pancreatitis (according to the revised Atlanta criteria) - All-cause mortality
Comparator instrument	Glasgow-Imrie score Predictors: 1. PaO_2 2. Age 3. White Blood Cell count 4. Serum calcium 5. Blood urea nitrogen (BUN) 6. Lactate dehydrogenase (LDH)

	7. Albumin 8. Glucose Predicted outcomes: - Severity (according to the revised Atlanta criteria) - All-cause mortality
Outcomes	Discrimination: - Area under the receiver-operator curve (AUC) Calibration: - Total observed versus expected events (O:E) ratio
Timing	Prognostic score assessed at hospital presentation or within 48 hours after hospital presentation
Setting	Hospital setting for early prognostic risk stratification of patients with acute pancreatitis.
Other selection criteria	Study design: systematic reviews, observational studies (prediction model development studies, prediction model validation studies)

Relevant outcome measures

The guideline panel considered area under the receiver-operator curve (AUC) and total observed versus expected events (O:E) ratio as a **critical** outcome measure for decision making.

The guideline panel considered definitions and thresholds for clinical relevance as defined in table 2.

Table 2. Definitions and thresholds

Outcome	Definition	Threshold
Critical outcome measures		
Severity of acute pancreatitis	Severity according to the revised Atlanta criteria. Mild pancreatitis: no local or systemic complications and no organ failure. Moderately severe acute pancreatitis: may include local or systemic complications or transient organ failure (≤48 hours). Severe acute pancreatitis: persistent organ failure >48 hours	As defined in the included studies.
All-cause mortality	All-cause mortality, in-hospital or within 6 months.	As defined in the included studies.
Discrimination	Area under the receiver operating characteristic curve (AUC).	0.7≤AUC<0.8: acceptable 0.8≤AUC<0.9: excellent AUC≥0.9: outstanding
Calibration	Agreement between the estimated and observed number of events, calculated as the natural logarithm of the total observed versus expected events ratio Ln(O:E)	No predefined threshold was used.

Search and select (Methods)

The guideline working group decided to adapt the recently published systematic literature review (Hann, 2026). A systematic literature search was performed using the following bibliographic databases: MEDLINE and Embase.com. The authors also searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). The search was originally performed on 9th July 2017, and then updated on 25th February 2020 and 26th May 2021 and 12th May 2023. The authors did not describe which study designs were searched. The overall search strategy is described in the original systematic review (Hann, 2026). After deduplication a total of 22,978 records were screened. Initially, 856 full-text articles were assessed for eligibility. In qualitative synthesis, 89 studies were included and 94 patient cohorts were included in quantitative synthesis (Hann 2026).

Summary of literature

Description of studies

A total of 89 studies, comprising 94 patients and 65,942 participants, were included in the analysis of the literature. Important study characteristics and results are summarized in table 3. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

The systematic review (Hann, 2026) evaluated prospective and retrospective studies assessing the APACHE II, Glasgow-Imrie, BISAP and Ranson scores in adults with acute pancreatitis. Inclusion criteria were: [1] availability of accuracy data for severity (according to the revised Atlanta criteria) and/or mortality (in-hospital mortality or mortality within 6 months), [2] application of prognostic scoring system <48 hours, with follow-up until discharge or 30 days, [3] studies reported as full text, those published as abstract only, and unpublished data. Studies in children (<18 years) were excluded. The accuracy of the prognostic models was reported on admission, within 24 hours of admission, within 48 hours of admission, and at 48 hours of admission. Included studies had follow-up until discharge or 30 days. Prognostic value was measured for severity of acute pancreatitis according to the revised Atlanta criteria (Bradley, 1993) and all-cause mortality. It was not specifically described which prognostic score was formally validated. The 89 studies were performed in hospital settings in 23 countries worldwide. A random-effects meta-analysis of the (logit transformed) AUC and the O:E ratio was performed for both SAP and mortality for each score.

Table 3. Characteristics of included studies

Study	Participants	Instrument	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Hann, 2026 *Details about the 94 included studies are presented in Supplementary*	N: 65,942 adults with acute pancreatitis, from 94 cohorts. N: 30 - 18,256 participants per cohort.	APACHE II Glasgow-Imrie BISAP Ranson	Until discharge, 30 days, or as defined in included studies.	Severe acute pancreatitis (according to revised Atlanta criteria) All-cause mortality	The researchers reported no funding for this research and no conflict of interest.	High risk of bias; no included study had low risk of bias across all domains.

Table 3.0 by Hann, 2026.	<u>APACHE II:</u> Admission: N=11 cohorts <24h: N=13 cohorts <48h: N=2 cohorts At 48h: - <u>Glasgow-Imrie:</u> Admission: N=5 cohorts <24h: - <48h: N=3 cohorts At 48h: N=4 cohorts Numbers of participants are not presented per prognostic score. Age (mean (range)): 52 years (30-72 years), reported in 76/94 studies. Sex (mean % female (range)): 44% (15-100%), reported in 87/94 studies. Event rate (%) is not presented per prognostic score or per study.	Predictors that are included in the instruments are not described by Hann, 2026.		AUC O:E ratio, where available.		Risk of bias was not presented per outcome measure.

*For further details, see risk of bias table in the appendix

<u>Results</u>

<u>Severity of acute pancreatitis (crucial)</u>

For *APACHE II*, the pooled AUC (95% CI) was 0.73 (0.70 to 0.76) at admission, 0.82 (0.78 to 0.85) within 24 hours and 0.81 (0.72 to 0.88) within 48 hours. This is clinically relevant within 24 and 48 hours, but the 95% confidence intervals overlap the limits of clinical relevance.

For *Glasgow-Imrie*, the pooled AUC (95% CI) was 0.77 (0.73 to 0.81) at admission, 0.88 (0.83 to 0.92) within 48 hours and 0.73 (0.65 to 0.80) at 48 hours. This is clinically relevant within 48 hours.

<u>All-cause mortality (crucial)</u>

For *APACHE II*, the pooled AUC (95% CI) was 0.83 (0.74 to 0.89) at admission, 0.86 (0.84 to 0.89) within 24 hours and 0.86 (0.80 to 0.91) within 48 hours. This is clinically relevant at all three timepoints, but the 95% confidence intervals overlap the limits of clinical relevance at admission and within 48 hours.

For *Glasgow-Imrie*, the pooled AUC (95% CI) was 0.88 (0.81 to 0.93) at admission and 0.82 (0.80 to 0.85) within 48 hours; data were not available for other time points. This is clinically relevant at both timepoints, but the 95% confidence interval overlaps the limits of clinical relevance within 48 hours.

5

Summary of Findings

Population: Adult patients with acute pancreatitis within 48h of hospital presentation

Index instrument: APACHE II score

Predicted outcome of the instrument:

- Severity (according to the revised Atlanta criteria)
- All-cause mortality

Comparator instrument: Glasgow-Imrie score

Predicted outcomes:

- Severity (according to the revised Atlanta criteria)
- All-cause mortality

Timing: Prognostic score assessed at hospital presentation or within 48 hours after hospital presentation.

Setting: Hospital setting for early prognostic risk stratification of patients with acute pancreatitis.

Outcome (performance measures)	**Study results and measurements**		**Certainty of the Evidence** (Quality of evidence)	**Conclusions**
	Index instrument (APACHE II)	**Comparator instrument (Glasgow-Imrie)**		
Discrimination: AUC at admission for severe acute pancreatitis (critical)	0.73 (95% CI 0.70 to 0.76)	0.77 (95% CI 0.73 to 0.81)	**Very low GRADE** [1]	The evidence is very uncertain about the discrimination properties at admission of the APACHE II score when compared to the Glasgow-Imrie score in predicting severe acute pancreatitis in patients with acute pancreatitis. (*Hann, 2026*)
	Based on data from 65,942 participants in 89 studies (94 cohorts).			
	Difference cannot be calculated as APACHE II and Glasgow-Imrie have not been compared in the same population			
Discrimination: AUC<24 hours for severe acute pancreatitis (critical)	0.82 (95% CI 0.78 to 0.85)	-	**No GRADE** (data was too limited to perform GRADE-analysis) [2]	Data was too limited about the discrimination properties of the APACHE II score within 24 hours when compared to the Glasgow-Imrie score in predicting severe acute pancreatitis in patients with acute pancreatitis. (*Hann, 2026*)
	Based on data from 65,942 participants in 89 studies (94 cohorts).			
	Difference cannot be calculated as APACHE II and Glasgow-Imrie have not been compared in the same population			
Discrimination: AUC <48 hours for severe acute pancreatitis (critical)	0.81 (95% CI 0.72 to 0.88)	0.88 (95% CI 0.83 to 0.92)	**Very low GRADE** [3]	The evidence is very uncertain about the discrimination properties within 48 hours of the APACHE II score when compared to the Glasgow-Imrie score in predicting severe acute pancreatitis in patients with acute pancreatitis. (*Hann, 2026*)
	Based on data from 65,942 participants in 89 studies (94 cohorts).			
	Difference cannot be calculated as APACHE II and Glasgow-Imrie have not been compared in the same population			
Discrimination: AUC at 48 hours for severe acute pancreatitis (critical)	-	0.73 (95% CI 0.65 to 0.80)	**No GRADE** (data was too limited to perform GRADE-analysis) [4]	Data was too limited about the discrimination properties of the APACHE II score at 48 hours when compared to the Glasgow-Imrie score in predicting severe acute pancreatitis in patients with acute pancreatitis. (*Hann, 2026*)
	Based on data from 65,942 participants in 89 studies (94 cohorts).			
	Difference cannot be calculated as APACHE II and Glasgow-Imrie have not been			

	compared in the same population			
Discrimination: AUC at admission for all-cause mortality (critical)	0.83 (95% CI 0.74 to 0.89)	0.88 (95% CI 0.81 to 0.93)	**Very low GRADE** [5]	The evidence is very uncertain about the discrimination properties at admission of the APACHE II score when compared to the Glasgow-Imrie score in predicting all-cause mortality in patients with acute pancreatitis. (*Hann, 2026*)
	Based on data from 65,942 participants in 89 studies (94 cohorts).			
	Difference cannot be calculated as APACHE II and Glasgow-Imrie have not been compared in the same population			
Discrimination: AUC <24 hours for all-cause mortality (critical)	0.86 (95% CI 0.84 to 0.89)	-	**No GRADE** (data was too limited to perform GRADE-analysis) [6]	Data was too limited about the discrimination properties of the APACHE II score within 24 hours when compared to the Glasgow-Imrie score in predicting all-cause mortality in patients with acute pancreatitis. (*Hann, 2026*)
	Based on data from 65,942 participants in 89 studies (94 cohorts).			
	Difference cannot be calculated as APACHE II and Glasgow-Imrie have not been compared in the same population			
Discrimination: AUC <48 hours for all-cause mortality (critical)	0.86 (95% CI 0.80 to 0.91)	0.82 (95% CI 0.80 to 0.85)	**Very low GRADE** [7]	The evidence is very uncertain about the discrimination properties within 48 hours of the APACHE II score when compared to the Glasgow-Imrie score in predicting all-cause mortality in patients with acute pancreatitis. (*Hann, 2026*)
	Based on data from 65,942 participants in 89 studies (94 cohorts).			
	Difference cannot be calculated as APACHE II and Glasgow-Imrie have not been compared in the same population			
Discrimination: AUC at 48 hours for all-cause mortality (critical)	-		**No GRADE** (no evidence was found)	No evidence was found about the calibration properties of the APACHE II score when compared to the Glasgow-Imrie score in predicting severe acute pancreatitis in patients with acute pancreatitis. (Hann, 2026)
Calibration: O/E ratio for severe acute pancreatitis (critical)	-	-	**No GRADE** (no evidence was found)	No evidence was found about the calibration properties of the APACHE II score when compared to the Glasgow-Imrie score in predicting severe acute pancreatitis in patients with acute pancreatitis. (Hann, 2026)
Calibration: O/E ratio for all-cause mortality	-	-	**No GRADE** (no evidence was found)	No evidence was found about the calibration properties of the APACHE II score when compared to the Glasgow-Imrie score in predicting mortality in patients with acute pancreatitis. (Hann, 2026)

*footnotes Certainty of the Evidence

1 Downgraded with two levels for Risk of Bias due to partly retrospective data-collection and unclear validation methodology and one level for Indirectness because a formal comparison between the two scores was not presented.

2 No comparison could be made between the two scores.

3 Downgraded with two levels for Risk of Bias due to partly retrospective data-collection and unclear validation methodology and one level for Indirectness because a formal comparison between the two scores was not presented.

4 No comparison could be made between the two scores.

5 Downgraded with two levels for Risk of Bias due to partly retrospective data-collection and unclear validation methodology and one level for Indirectness because a formal comparison between the two scores was not presented.

6 No comparison could be made between the two scores.

7 Downgraded with two levels for Risk of Bias due to partly retrospective data-collection and unclear validation methodology and one level for Indirectness because a formal comparison between the two scores was not presented.

Kennisvragen

Tijdens de ontwikkeling van deze module is systematisch naar onderzoeken gezocht die de zoekvraag kunnen beantwoorden. Door gebruik te maken van een systematische literatuuranalyse met beoordeling van de bewijskracht is duidelijk geworden dat er binnen deze module nog kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag:
Ondanks de beschikbaarheid van meerdere voorspellende scores voor de ernst van acute pancreatitis, blijven de negatief en positief voorspellende waardes van deze scores beperkt. Biomarkers gerelateerd aan inflammatie en/of acute pancreatitis zouden mogelijkerwijs bruikbaar kunnen zijn om in de toekomst beter de ernst van acute pancreatitis te voorspellen.

P: patiënten met acute pancreatitis
I: (nieuwe) biomarker
C: huidige voorspellende scores of biomarker(s)
O: ernst acute pancreatitis

Implementeren-tabel

Vraag	*Antwoord:* *Kruis aan en licht toe/ beschrijf*		*Toelichting keuze:*
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	In de praktijk bestaan meerdere prognostische scores en biomarkers voor het inschatten van de ernst van acute pancreatitis, maar het is onzeker welk instrument het meest geschikt is in de eerste 48 uur. Dit kan leiden tot variatie in de timing, keuze en interpretatie van risicostratificatie. De module beoogt duidelijk te maken dat geen enkele score of biomarker geïsoleerd gebruikt moet worden en dat klinische beoordeling en herhaalde evaluatie centraal staan.
	X	**Nieuwe evidentie**	Nieuwe evidentie bij reeds bestaand zwak bewijs
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
		< 5000	
	X	**5000-40.000**	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
	X	**Nee**	

I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		Zwak bewijs voor welke voorspeller voor ernst van ziekte het beste werkt	Grote noodzaak tot een goede voorspeller voor ernst van ziekte
Zorgverleners (artsen en verpleegkundigen)		Soms uitgebreide scores met meerdere variabelen, wat tijd kost om goed in te vullen.	Scores zijn opgebouwd uit gangbare variabelen die bekend zijn in deze populatie
Patiënt/ cliënt (naasten)		risicostratificatie kan ongerustheid geven of schijnzekerheid wekken.	Patiënten en naasten moeten begrijpen dat een score geen definitieve voorspelling is, maar een hulpmiddel naast klinische beoordeling.
Sociale context		Geen grote belemmering verwacht	De aanbeveling vraagt geen extra handelingen van de patiënt buiten de reguliere ziekenhuiszorg.
Organisatorische context		Verschillen tussen ziekenhuizen in beschikbaarheid van IL-6, EPD-ondersteuning en lokale afspraken.	Lokale werkafspraken over timing van beoordeling bij opname en herbeoordeling binnen 48 uur kunnen implementatie ondersteunen.
Financiële en juridische context		Geen belangrijke financiële of juridische belemmeringen verwacht.	De aanbeveling vereist geen aparte financiering.
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan)		**A**	**B**
		Patiënt/ cliënt (naaste)	Geen actieve handeling vereist, maar wel duidelijke uitleg over doel en

B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen? *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*			onzekerheid van risicostratificatie
	X	Professional	toepassen van risicostratificatie als aanvulling op klinische beoordeling, met herhaalde evaluatie van SIRS en CRP en zorgvuldige interpretatie van scores
	X	Beroepsvereniging, nl	Verspreiding van de aanbeveling via richtlijn, scholing en eventueel praktische hulpmiddelen
	X	Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	Faciliteren van lokale werkafspraken, tijdige beschikbaarheid van laboratoriumuitslagen en waar mogelijk EPD-ondersteuning voor scoreberekening
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	Direct toepasbaar.
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	De reguliere implementatieroutes lijken voldoende
		Ja *	

I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*	**X**	Nee	De aanbeveling betreft optimalisatie van bestaande ziekenhuiszorg en vraagt naar verwachting geen omvangrijke landelijke implementatie-impuls of zorginkoopafspraken

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is*

Literatuur

Bradley EL, 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg*. May 1993;128(5):586-90. doi:10.1001/archsurg.1993.01420170122019

Capurso G, Ponz de Leon Pisani R, Lauri G, Archibugi L, Hegyi P, Papachristou GI, Pandanaboyana S, Maisonneuve P, Arcidiacono PG, de-Madaria E. Clinical usefulness of scoring systems to predict severe acute pancreatitis: A systematic review and meta-analysis with pre and post-test probability assessment. United European Gastroenterol J. 2023 Nov;11(9):825-836. doi: 10.1002/ueg2.12464. Epub 2023 Sep 27. PMID: 37755341; PMCID: PMC10637128.

Hann, 2026, accepted. Referentie wordt toegevoegd wanneer deze is gepubliceerd.

Bijlagen bij module Voorspellen van de ernst van acute pancreatitis

Risk of Bias tables

See Hann, 2026

Literature search strategy

See Hann, 2026

Module 3. Vullingsbeleid bij acute pancreatitis

Literatuursamenvatting

Introduction (English)

Acute pancreatitis can cause SIRS (systemic inflammatory response syndrome) with vascular permeability. This is a potentially severe condition leading to hypoperfusion of vital organs including the pancreas and kidneys. The goal of fluid resuscitation therapy is to replenish the intravascular fluid deficit to prevent pancreas necrosis and kidney function loss. However, aggressive fluid resuscitation will result in fluid overload causing pulmonary and cardiac complications. Therefore, balancing these effects in acute pancreatitis is vital.

Search and select

A systematic review of the literature was performed to answer the following question(s): what are the effects of high-volume fluid infusion strategy versus low-volume fluid infusion strategy in patients with acute pancreatitis?

Table 1. PICO

Patients	Patients with acute pancreatitis
Intervention	Fluid infusion strategy high-volume
Control	Fluid infusion strategy low-volume
Outcomes	Mortality, new onset organ failure, pancreatic necrosis, comprehensive complication index, length of hospital stay, number of invasive interventions, severity pancreatitis
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Relevant outcome measures

The guideline panel considered mortality, new-onset organ failure and pancreatic necrosis as **critical** outcome measures for decision making; and comprehensive complication index, length of hospital stay, number of invasive interventions and severity pancreatitis as **important** outcome measures for decision making.

The guideline panel defined the outcome measures as follows:

- Mortality, defined as mortality during index admission
- Number of invasive interventions, defined as endoscopic, percutaneous or surgical interventions

A priori, the guideline panel did not define the other outcome measures listed above but used the definitions used in the studies.

The guideline panel defined the following thresholds for minimal clinically important differences:

- Mortality: a relative risk of ≤ 0.91 or ≥ 1.10;
- Other dichotomous outcome measures: a relative risk of ≤ 0.80 or ≥ 1.25;
- Continuous outcome measures: 0.5 x median baseline standard deviation (SD) or 0.5 x standardized mean difference (SMD).

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were

searched from 2005 to the 2nd of July 2025 for systematic reviews and RCTs Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from two primary search concepts: (1) acute pancreatitis; (2) fluid resuscitation. Duplicates were removed using EndNote software. After deduplication a total of 326 records were imported for title/abstract screening.

Initially, 23 studies were selected based on title and abstract screening. After reading the full text, 22 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and one study (Evans, 2024) was included.

Summary of literature

Description of studies

One study (Evans, 2024) was included in the analysis of the literature. Evans (2024) performed a systematic review and meta-analysis comparing aggressive versus non-aggressive intravenous fluid (IVF) therapy in patients with acute pancreatitis. They searched Medline, Central and Web of Science at November 23th 2023. All RCTs comparing the outcomes of aggressive IVF-therapy versus non-aggressive IVF-therapy in adult patients with acute pancreatitis of any cause were considered.

Evans (2024) included ten RCTs. The study of Wu (2011) was however not included in our literature analysis, since the control group did not receive non-aggressive fluid therapy but adjusted fluid therapy managed by their treating physician. Since the study of Liu (2021) does not seem to be published in a peer-reviewed journal, it was decided to exclude this study from our analysis.

Important study characteristics and results of the individual studies (N=8) included in Evans (2024) are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

Table 2. Characteristics of included studies in Evans (2024)

Study	Participants	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Mao (2009)	N at baseline I: 36 C: 40 Age (years ± SD) I: 51.3±14.3 C: 50.2±12.0 Male (n, %) I: NR C: NR Severity pancreatitis Severe	Definition I vs C I: 10–15 mL/kg/h C: 5–10 mL/kg/h Fluid volume in the first 24h (mL) I: 6855 C: 5841 Type of fluid Normal saline, Ringer's lactate, plasma, 6% hydroxyethyl starch (200 kD/o.5)	NR	Mortality	Funding and COI not reported in Evans (2024)	Some concerns (mortality)
Mao (2010)	N at baseline I: 56 C: 59 Age (years ± SD) I: 49.8±15.4 C: 48.8±10.1 Male (n, %) I: 34 (61) C: 36 (61) Severity pancreatitis Severe	Definition I vs C I: HCT < 35% C: HCT > 35% Fluid volume in the first 24h (mL) I: 4805 C: 3883 Type of fluid Normal saline, Ringer's lactate, plasma, 6% hydroxyethyl starch (200 kD/o.5)	NR	Mortality	Funding and COI not reported in Evans (2024)	Some concerns (mortality)

Buxbaum (2017)	N at baseline I: 27 C: 33 Age (years ± SD) I: 44.4±13.7 C: 45.3±12.3 Male (n, %) I: 21 (78) C: 24 (73) Severity pancreatitis Mild	Definition I vs C I: 20 mL/kg bolus followed by 3 mL/kg/h C: 10 mL/kg bolus followed by 1.5 mL/kg/h Fluid volume in the first 24h (mL) I: 5600 C: 3900 Type of fluid Ringers lactate	NR	Mortality, severity pancreatitis	Funding and COI not reported in Evans (2024)	Low (mortality), some concerns (severity pancreatitis)
Li (2019)	N at baseline I: 50 C: 50 Age (years ± SD) I: 44±10 C: 46±13 Male (n, %) I: 36 (72) C: 27 (54) Severity pancreatitis Mild	Definition I vs C I: 20 mL/kg bolus followed by 3 mL/kg/h C: 10 mL/kg bolus followed by 1.5 mL/kg/h Fluid volume in the first 24h (mL) I: NR C: NR Type of fluid NR	NR	Mortality	Funding and COI not reported in Evans (2024)	Some concerns (mortality)
Wang (2020)	N at baseline I: 52 C: 52 Age (years ± SD)	Definition I vs C I: 20 mL/kg bolus followed by 3 mL/kg/h C: 10 mL/kg bolus followed by 1.5 mL/kg/h Fluid volume in the first 24h (mL)	NR	Mortality	Funding and COI not reported in Evans (2024)	Some concerns (mortality)

	I: 43±1 C: 42±1 <u>Male (n, %)</u> I: 29 (55) C: 28 (54) <u>Severity pancreatitis</u> Mild	I: NR C: NR <u>Type of fluid</u> NR				
Cuéllar-Monterrubio (2020)	<u>N at baseline</u> I: 43 C: 45 <u>Age (years ± SD)</u> I: 36.7±15.9 C: 38.6±15.1 <u>Male (n, %)</u> I: 13 (30) C: 18 (40) <u>Severity pancreatitis</u> Mild to moderately severe	<u>Definition I vs C</u> I: 20 mL/kg bolus followed by 3 mL/kg/h for the first 24 h and then 30 mL/kg for the next 24 h C: 1.5 mL/kg/h for the first 24 h and 30 mL/kg during the next 24 h <u>Fluid volume in the first 24h (mL)</u> I: 6400 C: 2795 <u>Type of fluid</u> Ringers lactate	NR	Mortality, pancreatic necrosis, length of hospital stay	Funding and COI not reported in Evans (2024)	Low (mortality), some concerns (pancreatic necrosis) and high (length of hospital stay)
Angsubhakorn (2021)	<u>N at baseline</u> I: 22 C: 22 <u>Age (years ± SD)</u> I: 46.4±15.0 C: 45.0±15.0 <u>Male (n, %)</u>	<u>Definition I vs C</u> I: 20 mL/kg bolus followed by 3 mL/kg/h C: 10 mL/kg bolus followed by 1.5 mL/kg/h <u>Fluid volume in the first 24h (mL)</u> I: 4886 C: 3985 <u>Type of fluid</u>	NR	Mortality, length of hospital stay	Funding and COI not reported in Evans (2024)	Low (mortality) and high (length of hospital stay)

	I: 18 (82) C: 16 (73) <u>Severity pancreatitis</u> Mild	Ringers lactate				
de-Madaria (2022)	<u>N at baseline</u> I: 122 C: 127 <u>Age (years ± SD)</u> I: 56±18 C: 57±17 <u>Male (n, %)</u> I: 54 (44) C: 68 (54) <u>Severity pancreatitis</u> Mild	<u>Definition I vs C</u> I: 20 mL/kg bolus followed by 3 mL/kg/h C: 10 mL/kg bolus followed by 1.5 mL/kg/h <u>Fluid volume in the first 24h (mL)</u> I: 5400 C: 3310 <u>Type of fluid</u> Ringers lactate	NR	Mortality, new-onset organ failure, pancreatic necrosis, length of hospital stay, severity pancreatitis	Funding and COI not reported in Evans (2024). First interim analysis was planned after the enrolment of 248/744 patients. Based on the results, the trial was halted owing to worse results with respect to safety outcomes in the aggressive fluid therapy group. As a post hoc analysis, the Cochran–Mantel–Haenszel method with	Low (mortality), some concerns (pancreatic necrosis, new-onset organ failure and severity pancreatitis) and high (length of hospital stay)

					adjustment for randomization stratification factors (center, baseline presence or absence of SIRS, and baseline presence or absence of hypovolemia) was used.	

***For further details, see risk of bias table in the appendix**

C: comparison, HCT: hematocrit, I: intervention, NR: not reported, SD: standard deviation

Results

Mortality (crucial)

Evans (2024) reported on the outcome mortality, defined as overall mortality. In the aggressive fluid therapy group 34/408 (8%) patients died, compared to 15/428 (4%) patients in the non-aggressive fluid therapy (figure 1). Risk ratio (RR, 95%CI) was 2.40 (1.38 to 4.19), in favor of the non-aggressive fluid therapy group. This difference is clinically relevant.

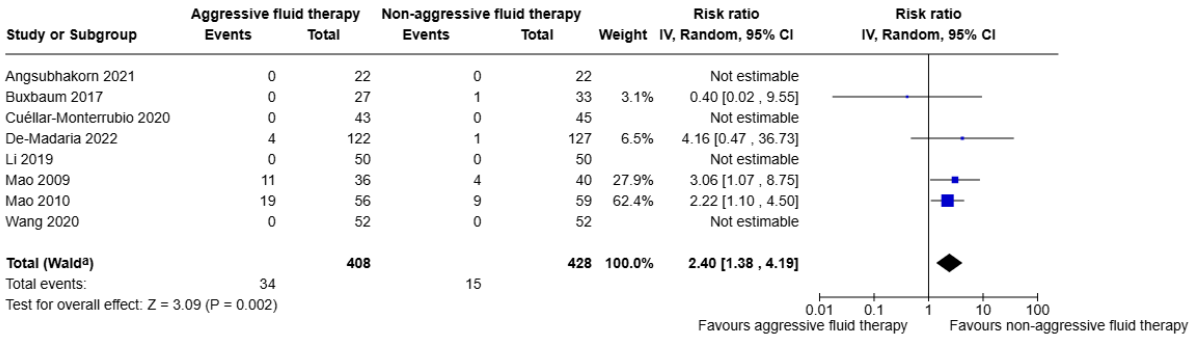


Figure 1: Forest plot on the effect of aggressive fluid therapy on mortality in patients with acute pancreatitis, compared to non-aggressive fluid therapy. Based on data in Evans (2024).

New onset organ failure (crucial)

Evans (2024) did not report on the outcome new-onset organ failure. Since this outcome was defined as a crucial outcome, we checked the individual studies whether they reported data on this outcome. Since the studies of Li (2019) and Wang (2020) were not available online, those studies could not be checked. De-Madaria (2022) reported on new-onset organ failure, which was defined as organ failure occurring after randomization and during hospitalization. Of the patients in the aggressive fluid therapy group 9/122 (7%) patients had new-onset organ failure, compared to 5/127 (4%) patients in het non-aggressive fluid therapy group. RR (95%CI) was 1.87 (0.65 to 5.43). Adjusted RR (95%CI) was 1.23 (0.47 to 3.23), in favor of the non-aggressive fluid therapy group. This difference is not clinically relevant.

(peri)Pancreatic necrosis (crucial)

Evans (2024) reported on the outcome pancreatic necrosis, which was not further defined. In the study of Cuéllar-Monterrubio (2020) 4/43 (9%) of the patients in the aggressive fluid therapy group had pancreatic necrosis, compared to 3/45 (7%) patients in het non-aggressive fluid therapy group. RR (95%CI) was 1.40 (0.33 to 5.87), in favor of the non-aggressive fluid therapy group. This difference is clinically relevant.

In the study of de-Madaria (2022) 17/122 (14%) of the patients in the aggressive fluid therapy group had pancreatic necrosis, compared to 9/127 (7%) patients in het non-aggressive fluid therapy group. RR (95%CI) was 1.97 (0.91 to 4.24), in favor of the non-aggressive fluid therapy group. This difference is clinically relevant.

Length of hospital stay (important)

Evans (2024) reported on the outcome length of hospital stay. Mean difference (95%CI) in length of hospital stay was 1.06 (0.0 to 2.12) days, in favor of the non-aggressive fluid therapy group (figure 2). This difference is clinically relevant.

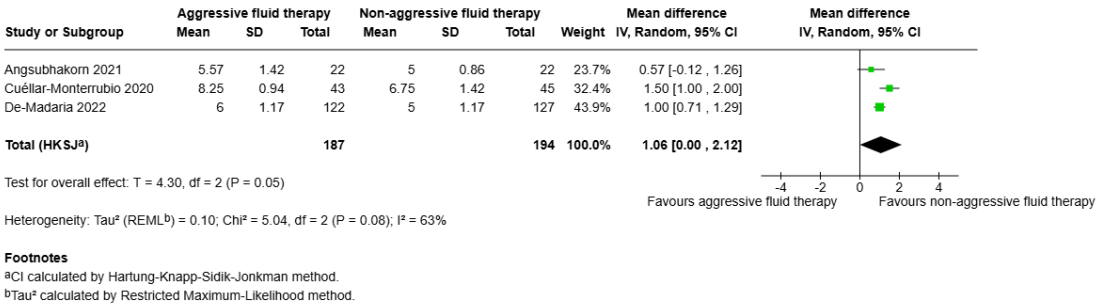


Figure 2: Forest plot on the effect of aggressive fluid therapy on length of hospital stay in patients with acute pancreatitis, compared to non-aggressive fluid therapy. Based on data in Evans (2024).

Quality of life (important)

Evans (2024) did not report on the outcome quality of life.

Number of invasive interventions (important)

Evans (2024) did not report on the outcome number of invasive interventions.

Comprehensive complication index (important)

Evans (2024) did not report on the outcome comprehensive complication index.

Severity pancreatitis (important)

Evans (2024) reported on the outcome severe pancreatitis, which was not further defined. In the study of Buxbaum (2017) 0/27 (0%) of the patients in the aggressive fluid therapy group had severe pancreatitis, compared to 1/23 (4%) patients in het non-aggressive fluid therapy group. RR (95%CI) was 0.29 (0.01 to 6.69), in favor of the aggressive fluid therapy group. However, due to very low number of events this RR is difficult to interpret.

In the study of De-Madaria (2022) 27/122 (22%) of the patients in the aggressive fluid therapy group had severe pancreatitis, compared to 22/127 (17%) patients in het non-aggressive fluid therapy group. RR (95%CI) was 1.28 (0.77 to 2.12), in favor of the non-aggressive fluid therapy group. This difference is clinically relevant.

Summary of Findings
Population: Patients with acute pancreatitis
Intervention: Aggressive fluid therapy
Comparator: Non-aggressive fluid therapy

5

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Non-aggressive fluid therapy*	Aggressive fluid therapy	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (crucial)	Relative risk: 2.40 (95%CI 1.38 - 4.19) Based on data from 836 participants in 8 studies	**4** per 1000	**10** per 1000 Difference: **6 more per 1000** (95%CI 2 more - 13 more)	**Moderate** Due to serious risk of bias[1]	Aggressive fluid therapy likely increases mortality when compared with non-aggressive fluid therapy in patients with acute pancreatitis.
New-onset organ failure (crucial)	Based on data from 249 participants in 1 study	Aggressive fluid therapy: 9/122 (7%) Non-aggressive fluid therapy: 5/127 (4%) Adjusted RR (95%CI): 1.23 (0.47 to 3.23).		**Very low** Due to serious risk of bias, due to very serious imprecision[2]	The evidence is very uncertain about the effect of aggressive fluid therapy on new-onset organ failure when compared with non-aggressive fluid therapy in patients with acute pancreatitis.
Pancreatic necrosis (crucial)	Based on data from 337 participants in 2 studies	*Cuéllar-Monterrubio (2020)* Aggressive fluid therapy: 4/43 (9%) Non-aggressive fluid therapy: 3/45 (7%) RR (95%CI): 1.40 (0.33 to 5.87) *De-Madaria (2022)* Aggressive fluid therapy: 17/122 (14%) Non-aggressive fluid therapy: 9/127 (7%) RR (95%CI): 1.97 (0.91 to 4.24)		**Low** Due to serious risk of bias, due to serious imprecision[3]	Aggressive fluid therapy may result in an increase in pancreatic necrosis when compared with non-aggressive fluid therapy in patients with acute pancreatitis.
Number of invasive interventions (important)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of aggressive fluid therapy on number

				of invasive interventions when compared with non-aggressive fluid therapy in patients with acute pancreatitis
Severity pancreatitis (important)	Based on data from 299 participants in 2 studies	*Buxbaum (2017)* Aggressive fluid therapy: 0/27 (0%) Non-aggressive fluid therapy: 1/23 (4%) (Due to low number of events, RR is difficult to interpret) *De-Madaria (2022)* Aggressive fluid therapy: 27/122 (22%) Non-aggressive fluid therapy: 22/127 (17%) RR (95%CI): 1.28 (0.77 to 2.12)	**Very low** Due to serious risk of bias, due to very serious imprecision[4]	The evidence is very uncertain about the effect of aggressive fluid therapy on severity of pancreatitis when compared with non-aggressive fluid therapy in patients with acute pancreatitis
Length of hospital stay (important)	Based on data from 381 participants in 3 studies	Difference: **MD 1.06 more** (95%CI 0.00 less - 2.12 more)	**Very low** Due to very serious risk of bias, due to serious imprecison[5]	The evidence is very uncertain about the effect of aggressive fluid therapy on length of hospital stay when compared with non-aggressive fluid therapy in patients with acute pancreatitis
Quality of life (important)	-	-	**No GRADE** (no evidence was found)	No evidence was found regarding the effect of aggressive fluid therapy on quality of life when compared with non-aggressive fluid therapy in patients with acute pancreatitis
Comprehensive complication index (important)	-	-	**No GRADE** (no evidence was found)	No evidence was found regarding the effect of aggressive fluid therapy on comprehensive complication index when compared

				with non-aggressive fluid therapy in patients with acute pancreatitis

1. *Risk of Bias: serious. Due to concerns regarding allocation concealment.*
2. *Risk of Bias: serious. Due to lack of blinding; Imprecision: very serious. Due to overlap of both limits of the 95% confidence interval with the minimal clinically important difference.*
3. *Risk of Bias: serious. Due to lack of blinding; Imprecision: serious. Due to overlap of the upper limit of the 95% confidence interval with the minimal clinically important difference.*
4. *Risk of Bias: serious. Due to lack of blinding; Imprecision: very serious. Due to overlap of both limits of the 95% confidence interval with the minimal clinically important difference.*
5. *Risk of Bias: very serious. Due to lack of blinding; Imprecision: serious. Due to overlap of the upper limit of the 95% confidence interval with the minimal clinically important difference.*

**Baseline/comparator Control arm of reference used for intervention. CI: confidence interval; RR: Risk ratio.*

Implementeren-tabel

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

Implementatietabel

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	
	x	**Nieuwe evidentie**	Na verschijnen van de laatste richtlijn zijn er nieuwe studies verschenen betreffende dit klinische vraagstuk.
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
		< 5000	
	x	**5000-40.000**	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?		**Ja**	
	x	Nee, kan als losstaande module worden beschouwd.	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		Geen belemmerende factoren	
Zorgverleners (artsen en verpleegkundigen)		Geen belemmerende factoren	
Patiënt/ cliënt (naasten)		Geen belemmerende factoren	

Sociale context		Geen belemmerende factoren	
Organisatorische context		Geen belemmerende factoren	Ringerlactaat is overal in NL beschikbaar
Financiële en juridische context		Geen belemmerende factoren	De zorgkosten nemen af met deze interventie
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
		Patiënt/ cliënt (naaste)	
	x	Professional	Volgen van richtlijn
	x	Beroepsvereniging, nl	Onder de aandacht brengen van de richtlijn bij SEH-artsen, intensivisten, chirurgen, ziekenhuisartsen en MDL-artsen
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**x**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	x	Nee	
		Ja *	

I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*	**x**	Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Kennisvragen

Tijdens de ontwikkeling van de module over vullingsbeleid is gebleken dat er binnen deze module de volgende kennisvraag bestaat:

Wat is de waarde van het toedienen van infuusvloeistof in vergelijking met ad libitum eten en drinken als er bij opname vanwege acute pancreatitis geen tekenen van hypovolemie zijn?
P: patiënten met acute pancreatitis in normovolemische toestand bij opname.
I: geen toediening van infuusvloeistof.
C: Ringerlactaat met een dosering van 1,5 ml/kg/uur.
O: mortaliteit, nieuw ontstaan orgaan falen, pancreasnecrose, duur ziekenhuisopname, Ernst pancreatitis, aantal interventies.

Literatuur

Angsubhakorn A, Tipchaichatta K, Chirapongsathorn S. Comparison of aggressive versus standard intravenous hydration for clinical improvement among patients with mild acute pancreatitis: A randomized controlled trial. Pancreatology. 2021 Oct;21(7):1224-1230. doi: 10.1016/j.pan.2021.06.004. Epub 2021 Jun 23. PMID: 34215499.

Buxbaum JL, Quezada M, Da B, Jani N, Lane C, Mwengela D, Kelly T, Jhun P, Dhanireddy K, Laine L. Early Aggressive Hydration Hastens Clinical Improvement in Mild Acute Pancreatitis. Am J Gastroenterol. 2017 May;112(5):797-803. doi: 10.1038/ajg.2017.40. Epub 2017 Mar 7. PMID: 28266591.

Cuéllar-Monterrubio JE, Monreal-Robles R, González-Moreno EI, Borjas-Almaguer OD, Herrera-Elizondo JL, García-Compean D, Maldonado-Garza HJ, González-González JA. Nonaggressive Versus Aggressive Intravenous Fluid Therapy in Acute Pancreatitis With More Than 24 Hours From Disease Onset: A Randomized Controlled Trial. Pancreas. 2020 Apr;49(4):579-583. doi: 10.1097/MPA.0000000000001528. PMID: 32282773.

Evans D, Hajibandeh S, Hajibandeh S, Athwal TS, Satyadas T. Meta-analysis and trial sequential analysis of randomized controlled trials comparing aggressive versus non-aggressive intravenous fluid therapy in acute pancreatitis: an insight into the existence of type 2 error. J Gastroenterol Hepatol. 2024 Oct;39(10):2018-2030. doi: 10.1111/jgh.16648. Epub 2024 Jun 13. PMID: 38872377.

IAP/APA/EPC/IPC/JPS Working Group. Electronic address: info@internationalpancreatology.org; IAP/APA/EPC/IPC/JPS Working Group. International Association of Pancreatology Revised Guidelines on Acute Pancreatitis 2025: Supported and Endorsed by the American Pancreatic Association, European Pancreatic Club, Indian Pancreas Club, and Japan Pancreas Society. Pancreatology. 2025 Sep;25(6):770-814. doi: 10.1016/j.pan.2025.04.020. Epub 2025 Jul 10. PMID: 40651900.

Li H. The value of early aggressive hydration in patients with mild acute pancreatitis. Chin J Emerg Med. 2020; 28: 794–7.

Liu J. Preliminary impact of the initial fluid resuscitation with different volume on the prognosis of acute pancreatitis not match the standard of severe AP. Master degree. Luzhou: Southwest Medical University, 2021.

de-Madaria E, Buxbaum JL, Maisonneuve P, García García de Paredes A, Zapater P, Guilabert L, Vaillo-Rocamora A, Rodríguez-Gandía MÁ, Donate-Ortega J, Lozada-Hernández EE, Collazo Moreno AJR, Lira-Aguilar A, Llovet LP, Mehta R, Tandel R, Navarro P, Sánchez-Pardo AM, Sánchez-Marin C, Cobreros M, Fernández-Cabrera I, Casals-Seoane F, Casas Deza D, Lauret-Braña E, Martí-Marqués E, Camacho-Montaño LM, Ubieto V, Ganuza M, Bolado F; ERICA Consortium. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med. 2022 Sep 15;387(11):989-1000. doi: 10.1056/NEJMoa2202884. PMID: 36103415

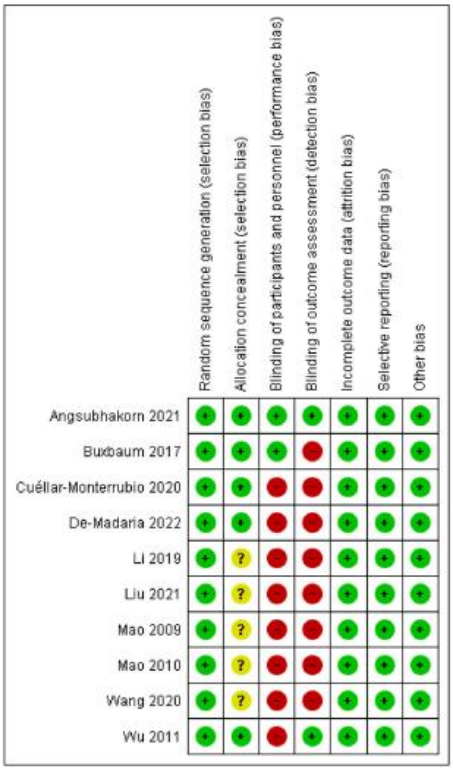
Mao EQ, Tang YQ, Fei J, Qin S, Wu J, Li L, Min D, Zhang SD. Fluid therapy for severe acute pancreatitis in acute response stage. Chin Med J (Engl). 2009 Jan 20;122(2):169-73. PMID: 19187641

Mao EQ, Fei J, Peng YB, Huang J, Tang YQ, Zhang SD. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. Chin Med J (Engl). 2010 Jul;123(13):1639-44. PMID: 20819621.

Wang SY. The application value of early aggressive hydration among patients with mild acute pancreatitis. Guangdong Med J. 2020; 41: 844–8.

Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, Smith B, Banks PA, Conwell DL. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol. 2011 Aug;9(8):710-717.e1. doi: 10.1016/j.cgh.2011.04.026. Epub 2011 May 12. PMID: 21645639.

Risk of Bias tables



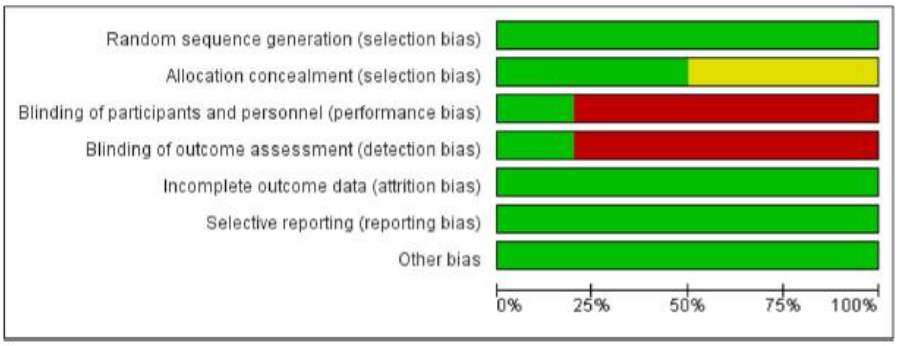


Figure 3: Risk of bias assessment using Cochrane Risk of Bias tool, adapted from Evans (2024). Green: low risk of bias, Yellow: unclear risk of bias, red: high risk of bias. The study of Wu (2011) and Liu (2021) are not included in the literature analysis.

Table of excluded studies

Reference	Reason for exclusion
Gad MM, Simons-Linares CR. Is aggressive intravenous fluid resuscitation beneficial in acute pancreatitis? A meta-analysis of randomized control trials and cohort studies. World J Gastroenterol. 2020 Mar 14;26(10):1098-1106. doi: 10.3748/wjg.v26.i10.1098. PMID: 32206000; PMCID: PMC7081000.	outdated SR
Di Martino M, Van Laarhoven S, Ielpo B, Ramia JM, Manuel-Vázquez A, Martínez-Pérez A, Pavel M, Beltran Miranda P, Orti-Rodríguez R, de la Serna S, Ortega Rabbione GJ, Sanz-Garcia A, Martín-Pérez E. Systematic review and meta-analysis of fluid therapy protocols in acute pancreatitis: type, rate and route. HPB (Oxford). 2021 Nov;23(11):1629-1638. doi: 10.1016/j.hpb.2021.06.426. Epub 2021 Jul 8. PMID: 34325967.	outdated SR
Liao J, Zhan Y, Wu H, Yao Z, Peng X, Lai J. Effect of aggressive versus conservative hydration for early phase of acute pancreatitis in adult patients: A meta-analysis of 3,127 cases. Pancreatology. 2022 Mar;22(2):226-234. doi: 10.1016/j.pan.2022.01.001. Epub 2022 Jan 5. PMID: 35031209.	outdated SR
Wu F, She D, Ao Q, Zhang S, Li J. Aggressive intravenous hydration protocol of Lactated Ringer's solution benefits patients with mild acute pancreatitis: A meta-analysis of 5 randomized controlled trials. Front Med (Lausanne). 2022 Sep 8;9:966824. doi: 10.3389/fmed.2022.966824. PMID: 36160176; PMCID: PMC9492986.	outdated SR
Dawson A, Karunakaran M, Sharma ZD, Ullah S, Barreto SG. Fluid resuscitation in the early management of acute pancreatitis - evidence from a systematic review and meta-analysis. HPB (Oxford). 2023 Dec;25(12):1451-1465. doi: 10.1016/j.hpb.2023.08.013. Epub 2023 Aug 29. PMID: 37689561.	No separate meta-analysis for RCT's (cohortstudies were included), more recent SR available.
Ding X, Chen B. Effect of Aggressive Intravenous Fluid Resuscitation Versus Nonaggressive Fluid Resuscitation in the Treatment of Acute Pancreatitis:	outdated SR

A Systematic Review and Meta-Analysis. Pancreas. 2023 Feb 1;52(2):e89-e100. doi: 10.1097/MPA.0000000000002230. PMID: 37523599.	
Guo J, Hong J, He Y, Li Q, Huang T, Lou D, Zhang J. Comparison of early aggressive versus nonaggressive fluid resuscitation in acute pancreatitis: a meta-analysis. Therap Adv Gastroenterol. 2023 Aug 22;16:17562848231192144. doi: 10.1177/17562848231192144. PMID: 37655061; PMCID: PMC10467253.	No separate meta-analysis for RCT's (cohortstudies were included)
He K, Gao L, Yang Z, Zhang Y, Hua T, Hu W, Wu D, Ke L. Aggressive versus controlled fluid resuscitation in acute pancreatitis: A systematic review and meta-analysis of randomized controlled trials. Chin Med J (Engl). 2023 May 20;136(10):1166-1173. doi: 10.1097/CM9.0000000000002684. Epub 2023 Apr 25. PMID: 37185290; PMCID: PMC10278702.	Focused on severe AP, more recent SR available
Li XW, Wang CH, Dai JW, Tsao SH, Wang PH, Tai CC, Chien RN, Shao SC, Lai EC. Comparison of clinical outcomes between aggressive and non-aggressive intravenous hydration for acute pancreatitis: a systematic review and meta-analysis. Crit Care. 2023 Mar 22;27(1):122. doi: 10.1186/s13054-023-04401-0. PMID: 36949459; PMCID: PMC10035244.	More recent SR available. Separate analyses for severe and non-severe AP.
Ehsan M, Ahmad AB, Javed H, Zahid A, Aamir HS, Cheema HA, Ayyan M, Mustafa B, Shahid A, Ilyas MA, Kandel K, Awan RU, Iqbal S. Aggressive Versus Moderate Fluid Replacement for Acute Pancreatitis: An Updated Systematic Review and Meta-Analysis. JGH Open. 2024 Dec 13;8(12):e70073. doi: 10.1002/jgh3.70073. PMID: 39678630; PMCID: PMC11645159.	No search strategy available
Kumari R, Sadarat F, Luhana S, Parkash O, Lohana AC, Rahaman Z, Wang HY, Mohammed YN, Kumar SK, Chander S. Evaluating the efficacy of different volume resuscitation strategies in acute pancreatitis patients: a systematic review and meta-analysis. BMC Gastroenterol. 2024 Mar 25;24(1):119. doi: 10.1186/s12876-024-03205-y. PMID: 38528470; PMCID: PMC10962108.	Makes a distinction between lo/moderate vs high; RoB assessment is not clear

Costea CN, Pojoga C, Seicean A. Advances in the Management of Fluid Resuscitation in Acute Pancreatitis: A Systematic Review. Diagnostics (Basel). 2025 Mar 22;15(7):810. doi: 10.3390/diagnostics15070810. PMID: 40218161; PMCID: PMC11988764.	No report of assessment RoB per study
Mao EQ, Tang YQ, Fei J, Qin S, Wu J, Li L, Min D, Zhang SD. Fluid therapy for severe acute pancreatitis in acute response stage. Chin Med J (Engl). 2009 Jan 20;122(2):169-73. PMID: 19187641.	Included in SR
Buxbaum JL, Quezada M, Da B, Jani N, Lane C, Mwengela D, Kelly T, Jhun P, Dhanireddy K, Laine L. Early Aggressive Hydration Hastens Clinical Improvement in Mild Acute Pancreatitis. Am J Gastroenterol. 2017 May;112(5):797-803. doi: 10.1038/ajg.2017.40. Epub 2017 Mar 7. PMID: 28266591.	Included in SR
Bolado F, Buxbaum JL, Vaillo-Rocamora A, Cárdenas-Jaén K, Maisonneuve P, de-Madaria E. Early Weight-Based Aggressive vs. Non-Aggressive Goal-Directed Fluid Resuscitation in the Early Phase of Acute Pancreatitis: An Open-Label Multicenter Randomized Controlled Trial (The WATERFALL Trial), Design, and Rationale. Front Med (Lausanne). 2020 Sep 2;7:440. doi: 10.3389/fmed.2020.00440. PMID: 32984361; PMCID: PMC7492535.	Study protocol
Cuéllar-Monterrubio JE, Monreal-Robles R, González-Moreno EI, Borjas-Almaguer OD, Herrera-Elizondo JL, García-Compean D, Maldonado-Garza HJ, González-González JA. Nonaggressive Versus Aggressive Intravenous Fluid Therapy in Acute Pancreatitis With More Than 24 Hours From Disease Onset: A Randomized Controlled Trial. Pancreas. 2020 Apr;49(4):579-583. doi: 10.1097/MPA.0000000000001528. PMID: 32282773.	Included in SR
Angsubhakorn A, Tipchaichatta K, Chirapongsathorn S. Comparison of aggressive versus standard intravenous hydration for clinical improvement among patients with mild acute pancreatitis: A randomized controlled trial. Pancreatology. 2021 Oct;21(7):1224-1230. doi:	Included in SR

10.1016/j.pan.2021.06.004. Epub 2021 Jun 23. PMID: 34215499.	
de-Madaria E, Buxbaum JL, Maisonneuve P, García García de Paredes A, Zapater P, Guilabert L, Vaillo-Rocamora A, Rodríguez-Gandía MÁ, Donate-Ortega J, Lozada-Hernández EE, Collazo Moreno AJR, Lira-Aguilar A, Llovet LP, Mehta R, Tandel R, Navarro P, Sánchez-Pardo AM, Sánchez-Marin C, Cobreros M, Fernández-Cabrera I, Casals-Seoane F, Casas Deza D, Lauret-Braña E, Martí-Marqués E, Camacho-Montaño LM, Ubieto V, Ganuza M, Bolado F; ERICA Consortium. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med. 2022 Sep 15;387(11):989-1000. doi: 10.1056/NEJMoa2202884. PMID: 36103415.	Included in SR
Mao EQ, Fei J, Peng YB, Huang J, Tang YQ, Zhang SD. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. Chin Med J (Engl). 2010 Jul;123(13):1639-44. PMID: 20819621.	Included in SR
Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, Smith B, Banks PA, Conwell DL. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol. 2011 Aug;9(8):710-717.e1. doi: 10.1016/j.cgh.2011.04.026. Epub 2011 May 12. PMID: 21645639.	Included in SR
Froghi F, Soggiu F, Ricciardi F, Vindrola-Padros C, Floros L, Martin D, Filipe H, Varcada M, Gurusamy K, Bhattacharya S, Fanshawe A, Delcea B, Mathur P, Davidson B; GAP Collaborators. Ward based goal directed fluid therapy (GDFT) in acute pancreatitis (GAP) trial: A feasibility randomised controlled trial. Int J Surg. 2022 Aug;104:106737. doi: 10.1016/j.ijsu.2022.106737. Epub 2022 Jul 12. PMID: 35835346.	Wrong comparison
Bashir N, Shamsudeen MP, Kuchay AA. Assessment of Cardiovascular Status and Hemodynamics in Patients of Severe Acute Pancreatitis on Liberal Vs Restrictive Fluid Therapy. Int J of Life Sciences	Wrong study design (prospective study), full tekst not available online

Biotechnology and Pharma Research. 2024 Jan; 13 (12): 984-988. **https://doi.org/10.69605/ijlbpr_13.12.2024.182**	

Literature search strategy

5 ***Zoekstrategie Embase.com 2 juli 2025***

No.	*Query*	*Results*
#1	**'acute pancreatitis'/exp OR 'acute hemorrhagic pancreatitis'/exp OR (('pancreatitis'/exp OR pancreatit*:ti,ab,kw OR ((pancrea* NEAR/3 inflammation*):ti,ab,kw)) AND ('acute disease'/exp OR acut*:ti,ab,kw))**	**73060**
#2	**'fluid therapy'/de OR 'fluid resuscitation'/exp OR 'rehydration'/de OR 'infusion fluid'/exp OR 'fluid intake'/exp OR 'fluid balance'/exp OR 'crystalloid'/exp OR ((fluid* NEAR/3 (therap* OR management* OR replacement*)):ti,ab,kw) OR (((ringer* OR saline* OR hartmann*) NEAR/3 (lactate* OR solution*)):ti,ab,kw) OR (((infus* OR intraven* OR 'intra venous' OR iv) NEAR/3 (fluid* OR liquid* OR therap*)):ti,ab,kw) OR (((aggressive* OR highvolume* OR 'high volume*') NEAR/3 (hydrati* OR rehydrati*)):ti,ab,kw) OR ((fluid* NEAR/3 (aggressive* OR overload*)):ti,ab,kw) OR resuscitat*:ti,ab,kw OR crystalloid*:ti,ab,kw OR hemoconcentration*:ti,ab,kw OR colloid*:ti,ab,kw OR 'normal saline*':ti,ab,kw OR 'sodium chloride*':ti,ab,kw OR dextran:ti,ab,kw**	**590354**
#3	**#1 AND #2**	**4756**
#4	**#3 AND [2005-2025]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'clinical trial':dtype) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)**	**1994**
#5	**'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw)**	**1134388**

	OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	
#6	**'randomized controlled trial'/exp OR (((pragmatic OR practical) NEAR/1 'clinical trial'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEXT/3 trial):ti,ab) OR rct:ti OR randomly*:ti,ab OR randomi*:ti,ab OR 'random* control*':ti,ab**	**2183950**
#7	**#4 AND #5 - SR**	**134**
#8	**#4 AND #6 NOT #7 - RCT**	**152**
#9	**#7 OR #8 - Totaal**	**286**

Zoekstrategie Ovid/Medline 2 juli 2025

#	Searches	Results
1	**exp Pancreatitis, Acute Hemorrhagic/ or exp Pancreatitis, Acute Necrotizing/ or ((exp Pancreatitis/ or pancreatit*.ti,ab,kf. or (pancrea* adj3 inflammation*).ti,ab,kf.) and (exp Acute Disease/ or acut*.ti,ab,kf.))**	**41752**
2	**exp Fluid Therapy/ or Resuscitation/ or exp Infusions, Intravenous/ or Water-Electrolyte Balance/ or exp Crystalloid Solutions/ or (fluid* adj3 (therap* or management* or replacement*)).ti,ab,kf. or ((ringer* or saline* or hartmann*) adj3 (lactate* or solution*)).ti,ab,kf. or ((infus* or intraven* or intra venous or iv) adj3 (fluid* or liquid* or therap*)).ti,ab,kf. or ((aggressive* or highvolume* or high volume*) adj3 (hydrati* or rehydrati*)).ti,ab,kf. or (fluid* adj3 (aggressive* or overload*)).ti,ab,kf. or resuscitat*.ti,ab,kf. or crystalloid*.ti,ab,kf. or hemoconcentration*.ti,ab,kf. or colloid*.ti,ab,kf. or normal saline*.ti,ab,kf. or sodium chloride*.ti,ab,kf. or dextran.ti,ab,kf.**	**442736**

3	**1 and 2**	**1727**
4	**limit 3 to yr="2005 -Current"**	**1168**
5	**4 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)**	**971**
6	**exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.**	**841910**
7	**exp randomized controlled trial/ or randomi*.ti,ab. or rct?.ti,ab. or randomly.ti,ab. or "random* control*".ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab.**	**1447137**
8	**5 and 6 - SR**	**78**
9	**(5 and 7) not 8 - RCT**	**111**
10	**8 or 9 - Totaal**	**189**

5

Module 4. Voedingsbeleid bij acute pancreatitis

Introduction (English)

Nausea, vomiting, and impaired gastrointestinal transit are - beyond pain - frequently observed symptoms in acute pancreatitis (AP). While these symptoms may be transient during the initial phase, they can persist due to gastropareses or local complications, leading to an inability to maintain adequate oral intake.

Consequently, nutritional interventions are commonly initiated during AP, aiming to optimize nutritional status and, hypothetically, to attenuate disease severity. However, the optimal timing and route of nutritional support remain partially unclear, contributing to variability in clinical practice. In addition, the overall impact of nutritional strategies on clinical outcomes remains partially unresolved in the current literature.

Search and select

A systematic review of the literature was performed to answer the following question(s): What are the (un)beneficial effect of early nutritional support (< 24 hours after admission) instead of the ad libitum normal diet only supplemented with nutritional support > 72 hours after admission in adult patients with acute pancreatitis?

Table 1. PICO

Patients	Patients with acute pancreatitis
Intervention	Early nutritional support (< 24 hours after admission; both oral as (par)enteral)
Control	Ad libitum normal diet only supplemented with nutritional support > 72 hours after admission; both oral as (par)enteral
Outcomes	Mortality, infected pancreatic necrosis, new-onset organ failure, severity of pancreatitis, length of hospital stay, comprehensive complication index, quality of life, number of invasive interventions, and exocrine pancreatic insufficiency
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Relevant outcome measures

The guideline panel considered mortality, infected pancreatic necrosis, new-onset organ failure and severity of pancreatitis as **critical** outcome measures for decision making; and comprehensive complication index, length of hospital stay, quality of life, number of invasive interventions and exocrine pancreatic insufficiency as **important** outcome measures for decision making.

The guideline panel defined the outcome measures as follows:

- Mortality, defined as mortality during index admission
- Number of invasive interventions, defined as endoscopic, percutaneous or surgical interventions

A priori, the guideline panel did not define the other outcome measures listed above but used the definitions used in the studies.

The guideline panel defined the following thresholds for minimal clinically important differences:

- Mortality: a relative risk of ≤ 0.90 or ≥ 1.10;
- Other dichotomous outcome measures: a relative risk of ≤ 0.80 or ≥ 1.25;
- Continuous outcome measures: 0.5 x median baseline standard deviation (SD) or 0.5 x standardized mean difference (SMD).

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2005 to 22nd of July 2025 for systematic reviews and RCTs. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from two primary search concepts: (1) acute pancreatitis; (2) nutritional support. Duplicates were removed using EndNote software. After deduplication a total of 903 records were imported for title/abstract screening.

Titles and abstracts were screened using the ASReview software. The settings ELAS u4 (TF-IDF and SVM) were used. Liu (2023) and Bakker (2014) were used as prior knowledge for inclusion. Pandapotan (2025) and Schepers (2016) were used as prior knowledge for exclusions. The articles were subsequently screened by the guideline methodologist, using the following stopping rule: stop after 10% of the total set subsequent exclusions. Initially, 34 studies were selected based on title and abstract screening. After reading the full text, 33 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and one study was included.

Summary of literature

Description of studies

One study was included in the analysis of the literature (Bakker, 2014). Bakker (2014) performed a multicenter randomized controlled trial (RCT) in het Netherlands, to evaluate the effect of early nutritional support (<24h) versus an oral diet initiated >72h in patients with acute pancreatitis. Adult patients with acute pancreatitis and having a high risk for complications were eligible for inclusion in the study. University medical centers (N=6) and large teaching hospitals (N=13) of the Dutch Pancreatitis Study Group participated in the study. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

Table 2. Characteristics of included study

Study	Participants	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)****
Bakker, 2014	N at baseline* I: 101 C: 104 Age (years ± SD) I: 65±16 C: 65±15 Female (n, %)	I: nasoenteric (nasajejunal) tube feeding initiated <24h after randomization**. Started at 20 ml per hour during the first 24h and	6 months ***	Mortality, infected pancreatic necrosis, new-onset organ failure	Supported by grants from the Netherlands Organization for Health Research and Development, the ZonMw Health Care Efficiency	

	I: 46 (46) C: 45 (43) <u>Severity pancreatitis</u> *APACHE II-score (mean*±SD) I: 11±4 C: 11±5 *Glasgow score (median (range))* I: 2 (0-6) C: 2 (0-5) *SIRS (n(%))* I: 63 (62) C: 70 (67) *Multiple organ failure (n(%))* I: 6 (6) C: 5 (5)	increased gradually C: oral diet starting at 72h, except for patients who requested oral food during the first 72h. If an oral diet was not tolerated >96h nasoenteric (nasajejunal) feeding was started.			Research Program and Nutricia None of the patients was lost to follow-up.	

<u>Results</u>

Mortality (critical)

Bakker (2014) reported on the outcome mortality. In the early tube feeding group 11/101 (11%) patients died, compared to 7/104 (7%) in the delayed feeding group. Risk ratio (RR, 95%CI) was 1.27 (0.85 to 1.89), in favor of the delayed feeding group. This difference is clinically relevant.

New-onset organ failure (critical)

Bakker (2014) reported on the outcome new-onset organ failure, which was defined as a modified Marshall score ≥ 2 which was not present at randomization. Results are reported in table 3. In total, 47/67 (70%) of the patients in the early tube feeding group had new-onset organ failure, compared to 51/73 (70%) in the delayed feeding group. RR (95C%CI) was 1 (0.81 to 1.25).

Table 3: Development of new-onset organ failure in patients with acute pancreatitis, receiving early tube feeding or delayed feeding (Bakker, 2014).

New-onset organ failure	Early tube feeding group (n/N* (%))	Delayed feeding group (n/N* (%))	Risk ratio (95%CI)
Single organ failure	26/67 (39)	31/73 (42)	0.92 (0.65–1.32)
Persistent single organ failure	10/67 (15)	10/73 (14)	1.05 (0.65–1.70)
Multiple organ failure**	7/67 (10)	6/73 (8)	1.14 (0.67–1.95)
Persistent multiple organ failure***	4/67 (6)	4/73 (5)	1.05 (0.51–2.14)

***Number of patients at risk. **Defined as organ failure present on 3 or more consecutive days (>48 hours). *** Defined as failure of two or more organs on the same day.**

Infected pancreatic necrosis (critical)

Bakker (2014) reported on the outcome infected pancreatic necrosis, which was defined as positive culture of pancreatic or extrapancreatic necrotic tissue obtained with fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the fluid collection on contrast-enhanced CT. In the early tube feeding group 9/101 (9%) patients had infected pancreatic necrosis, compared to 15/104 (14%) in the delayed feeding group. RR (95%CI) was 0.74 (0.43 to 1.26), in favor of the early tube feeding group. This difference is clinically relevant.

Severity of pancreatitis (critical)

Bakker (2014) reported on the outcome severity of pancreatitis, determined by the CT severity index. In the early tube feeding group mean (±SD) score was 4±2, compared to 4±3 in the delayed feeding group. Mean difference (95%CI) was 0 (-0.7 to 0.7). This difference is not clinically relevant.

Length of hospital stay (important)

Bakker (2014) reported on the outcome length of hospital stay, which also included readmissions. In the early tube feeding group median (IQR) length of hospital stay was 15 (10 to 22) days, compared to 14 (9 to 25) days in the delayed feeding group.

Comprehensive complication index (important)

Bakker (2014) did not report on the outcome comprehensive complication index.

Quality of life (important)

Bakker (2014) did not report on the outcome quality of life.

Number of invasive interventions (important)

Bakker (2014) reported on the outcome number of invasive interventions: endoscopic retrograde cholangiopancreaticography (ERCP), percutaneous catheter drainage, endoscopic transgastric drainage or necrosectomy, surgical necrosectomy and other interventions (e.g. cholecystectomy for biliary pancreatitis). Results are reported in table 4. In the early tube feeding group (N=101) the total number of invasive interventions was 111, compared to 158 in the delayed feeding group (N=104).

Table 4. Number of invasive interventions in patients with acute pancreatitis, receiving early tube feeding or delayed feeding (Bakker, 2014).

Intervention	Early tube feeding group (n (range per patient)), N=101	Delayed feeding group (n (range per patient)), N=104
ERCP	37 (0-3)	50 (0-6)
Percutaneous catheter drainage	24 (0-3)	46 (0-15)
Endoscopic transgastric drainage or necrosectomy	8 (0-7)	6 (0-2)
Surgical necrosectomy	3 (0-1)	7 (0-2)
Other interventions	39 (0-3)	49 (0-3)

ERCP: endoscopic retrograde cholangiopancreaticography

Exocrine pancreatic insufficiency (important)

Bakker (2014) reported on the outcome exocrine pancreatic insufficiency. In the early tube feeding group 0/101 (0%) patients had exocrine pancreatic insufficiency, compared to 2/104 (2%) in the delayed feeding group. RR (95%CI) was 0.21 (0.01 to 4.24), which is however difficult to interpret due to very low number of/no events.

Summary of findings

Population: Acute pancreatitis

Intervention: Early nutritional support (< 24 hours after admission; both oral as (par)enteral)

Comparator: Ad libitum normal diet only supplemented with nutritional support > 72 hours after admission; both oral as (par)enteral

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Ad libitum _ delayed nutritional support*	Early nutritional support	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (critical)	Relative risk: 1.27 (CI 95% 0.85 - 1.89) Based on data from 205 participants in 1 study Follow up 6 months	**67** per 1000	**85** per 1000 Difference: **18 more per 1000** (CI 95% 10 fewer - 60 more)	**Very low** Due to very serious imprecision[1]	The evidence is very uncertain about the effect of early nasojejunal tube feeding on mortality when compared with delayed feeding in patients with acute pancreatitis.
New-onset organ failure (critical)	Relative risk: 1.0 (CI 95% 0.81 - 1.25) Based on data from 140 participants in 1 study Follow up 6 months	**699** per 1000	**699** per 1000 Difference: **0 fewer per 1000** (CI 95% 133 fewer - 175 more)	**Low** Due to serious risk of bias, due to serious imprecision[2]	Early nasojejunal tube feeding may result in little to no difference in new-onset organ failure when compared with delayed feeding in patients with acute pancreatitis.
Infected pancreatic necrosis (critical)	Relative risk: 0.74 (CI 95% 0.43 - 1.26) Based on data from 205 participants in 1 study Follow up 6 months	**144** per 1000	**107** per 1000 Difference: **37 fewer per 1000** (CI 95% 82 fewer - 37 more)	**Very low** Due to serious risk of bias, due to very serious imprecision[3]	The evidence is very uncertain about the effect of early nasojejunal tube feeding on infected pancreatic necrosis when compared with delayed feeding in

				patients with acute pancreatitis.
Severity of pancreatitis (critical)	Lower beter Based on data from 205 participants in 1 study. Follow-up 6 months	Mean: 4±2	Mean: 4±3	**Low** Due to very serious risk of bias[4]	Early nasojejunal tube feeding may result in little to no difference in severity of pancreatitis when compared with delayed feeding in patients with acute pancreatitis.
		Difference: 0 lower (MD) (CI 95% 0.7 lower to 0.7 higher)			
Length of hospital stay (important)	Based on data from 205 participants in 1 study. Follow up 6 months.	In the early tube feeding group median (IQR) length of hospital stay was 15 (10 to 22) days, compared to 14 (9 to 25) days in the delayed feeding group.		**No GRADE** (data was too limited to perform GRADE-analysis)	Data was too limited regarding the effect of early nasojejunal tube feeding on length of hospital stay when compared with delayed feeding in patients with acute pancreatitis
Comprehensive complication index (important)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of early nasojejunal tube feeding on comprehensive complication index when compared with delayed feeding in patients with acute pancreatitis
Number of invasive interventions (important)	Based on data from 205 participants in 1 study. Follow up 6 months.	In the early tube feeding group (N=101) the total number of invasive interventions was 111, compared to		**No GRADE** (data was too limited to perform GRADE-analysis)	Data was too limited regarding the effect of early nasojejunal tube feeding on

		158 in the delayed feeding group (N=104).		number of invasive interventions when compared with delayed feeding in patients with acute pancreatitis
Quality of life (important)	-	-	**No GRADE** (no evidence was found)	No evidence was found regarding the effect of early nasojejunal tube feeding on quality of life when compared with delayed feeding in patients with acute pancreatitis
Exocrine pancreatic insufficiency (important)	Based on data from 205 participants in 1 study Follow up 6 months	In the early tube feeding group 0/101 (0%) patients had exocrine pancreatic insufficiency, compared to 2/104 (2%) in the delayed feeding group. Due to low number of events, effect measure is difficult to interpret.	**Very low** Due to serious risk of bias, due to very serious imprecision[5]	The evidence is very uncertain about the effect of early nasojejunal tube feeding on exocrine pancreatic insufficiency when compared with delayed feeding in patients with acute pancreatitis.

6. **Imprecision: serious.** Due to overlap of the upper limit of the 95% confidence interval with the minimal clinically important difference.
7. **Risk of Bias: serious.** Due to lack of blinding, **Imprecision: serious.** Due to overlap of the lower limit of the 95% confidence interval with the minimal clinically important difference.
8. **Risk of Bias: serious.** Due to lack of blinding, **Imprecision: serious.** Due to overlap of both limits of the 95% confidence interval with the minimal clinically important difference.
9. **Risk of Bias:** very serious. Due to lack of blinding.
10. **Risk of Bias: serious.** Due to lack of blinding, **Imprecision: very serious.** Optimal information size (OIS) is not met.

*__Baseline/comparator__ Control arm of reference used for intervention.

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag:
Wat is het optimale voedingsbeleid bij patiënten waarbij tussen 24 uur en 72 uur na het ontstaan van de acute pancreatitis orale voeding niet (voldoende) getolereerd wordt of onmogelijk is?

P: Patients with acute pancreatitis
I: Nutritional support (between 24 to 72hours after admission; both oral as (par)enteral)
C: Ad libitum normal diet only supplemented with nutritional support > 72 hours after admission; both oral as (par)enteral
O: Mortality, infected pancreatic necrosis, new-onset organ failure, severity of pancreatitis, length of hospital stay, comprehensive complication index, quality of life, number of invasive interventions, and exocrine pancreatic insufficiency

Implementeren-tabel
De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

Implementatietabel

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?		**Ongewenste praktijkvariatie**	
		Nieuwe evidentie	
	x	**Anders**	Knelpunt in de praktijk. Discussie wanneer er gestart kan worden met voeding en wat voor voeding dit moet zijn (oraal, sondevoeding of parenteraal).
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
		< 5000	
	x	**5000-40.000**	
		> 40.000	
		Ja	

I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?	**X**	**Nee**	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)			
Zorgverleners (artsen en verpleegkundigen)		Terughoudendheid met starten van voeding of voedingsinterventie	Sneller herstel door betere voedingsinname wat de opnameduur kan verkorten en complicaties kan voorkomen
Patiënt/ cliënt (naasten)		Niet willen starten met dieetpreparaten/sondevoeding	Uitleg en onderbouwing waarom dit geadviseerd wordt door arts en diëtist
Sociale context			
Organisatorische context			
Financiële en juridische context			
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan*		**A**	**B**
	X	Patiënt/ cliënt (naaste)	Begrip om eerste paar dagen proberen op eigen kracht te eten. Als dit faalt te accepteren dat de noodzaak is tot enteraal voeden

aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.			met de belasting van een sonde.
	X	Professional	Bereidheid om in de eerste paar dagen normale voedsel inname te stimuleren. Maar als dit onvoldoende blijk te zijn na 72u, door te pakken naar sondevoeding of parenterale voeding.
	X	Beroepsvereniging, nl	Bereidheid om een pro-actief en gelaagd voedingsbeleid te ondersteunen en uit te dragen.
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	
		Ja *	

I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*	**x**	Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Literatuur

Arvanitakis M, Ockenga J, Bezmarevic M, Gianotti L, Krznarić Ž, Lobo DN, Löser C, Madl C, Meier R, Phillips M, Rasmussen HH, Van Hooft JE, Bischoff SC. ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. Clin Nutr. 2020 Mar;39(3):612-631. doi: 10.1016/j.clnu.2020.01.004. Epub 2020 Jan 22. PMID: 32008871.

Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, Dejong CH, van Goor H, Bosscha K, Ahmed Ali U, Bouwense S, van Grevenstein WM, Heisterkamp J, Houdijk AP, Jansen JM, Karsten TM, Manusama ER, Nieuwenhuijs VB, Schaapherder AF, van der Schelling GP, Schwartz MP, Spanier BW, Tan A, Vecht J, Weusten BL, Witteman BJ, Akkermans LM, Bruno MJ, Dijkgraaf MG, van Ramshorst B, Gooszen HG; Dutch Pancreatitis Study Group. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. N Engl J Med. 2014 Nov 20;371(21):1983-93. doi: 10.1056/NEJMoa1404393. PMID: 25409371.

Dutta AK, Goel A, Kirubakaran R, Chacko A, Tharyan P. Nasogastric versus nasojejunal tube feeding for severe acute pancreatitis. Cochrane Database Syst Rev. 2020 Mar 26;3(3):CD010582. doi: 10.1002/14651858.CD010582.pub2. PMID: 32216139; PMCID: PMC7098540.

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Liu Y, Wan Z, Liao D. Efficacy of enteral nutrition for patients with acute pancreatitis: A systematic review and meta analysis of 17 studies. Exp Ther Med. 2023 Mar 13;25(4):184. doi: 10.3892/etm.2023.11883. PMID: 37021072; PMCID: PMC10067544.

Pandapotan RA, Syafitri A, Setiawan A, Gunawan B, Citra NG, Bierhuijs JA, Titus J. Early Enteral Feeding Versus Total Parenteral Feeding After Surgery in Severe Acute Pancreatitis: An Evidence-Based Case Report. Acta Med Indones. 2025 Apr;57(2):275-283. PMID: 40641197.

Schepers NJ, Bakker OJ, Besselink MG, Bollen TL, Dijkgraaf MG, van Eijck CH, Fockens P, van Geenen EJ, van Grinsven J, Hallensleben ND, Hansen BE, van Santvoort HC, Timmer R, Anten MP, Bolwerk CJ, van Delft F, van Dullemen HM, Erkelens GW, van Hooft JE, Laheij R, van der Hulst RW, Jansen JM, Kubben FJ, Kuiken SD, Perk LE, de Ridder RJ, Rijk MC, Römkens TE, Schoon EJ, Schwartz MP, Spanier BW, Tan AC, Thijs WJ, Venneman NG, Vleggaar FP, van de Vrie W, Witteman BJ, Gooszen HG, Bruno MJ; Dutch Pancreatitis Study Group. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial. Trials. 2016 Jan 5;17:5. doi: 10.1186/s13063-015-1132-0. PMID: 26729193; PMCID: PMC4700728.

Zhu Y, Yin H, Zhang R, Ye X, Wei J. Nasogastric Nutrition versus Nasojejunal Nutrition in Patients with Severe Acute Pancreatitis: A Meta-Analysis of Randomized Controlled Trials. Gastroenterol Res Pract. 2016;2016:6430632. doi: 10.1155/2016/6430632. Epub 2016 Jun 2. PMID: 27340401; PMCID: PMC4909901.

Bijlagen bij module Voedingsbeleid

Risk of Bias tables

Risk of bias table for intervention studies (randomized controlled trials; based on Cochrane risk of bias tool and suggestions by the CLARITY Group at McMaster University)

Research question: What are the (un)beneficial effect of early nutrition (< 24 hours after admission) instead of the ad libitum normal diet only supplemented with nutritional support > 72 hours after admission in adult patients with acute pancreatitis?

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Bakker, 2014	Definitely yes; Reason: Randomization was performed centrally by the study coordinator with the use of a Web-based system.	Definitely yes; Reason: Randomization was performed with the use of a Web-based system that used permuted-block randomization with a concealed, varying block size.	Definitely no/probably yes; Reason: Patients and health care providers were not blinded. Data collectors: Adjudication committee that evaluated primary endpoint and radiologist who interpreted	Definitely yes; Reason: no lost to follow-up	Definitely yes; Reason: almost al of the predefined outcome measures were reported (except for some secondary outcome measures (like use of antibiotics, quality	Definitely yes; Reason: No other problems noted (Sponsors were not involved in the design or conduct of the study, manuscript preparation or decision to submit it	**LOW** (mortality, infected pancreatic necrosis) **Some concerns** (new-onset organ failure, severity of pancreatitis and exocrine pancreatic insufficiency) **HIGH** (length of hospital stay and number of invasive interventions)

			CT-studies were unaware of treatment assignment. Other data collectors might not have been blinded, but 10% of data was randomly checked by independent auditor Not reported whether data analysts were blinded, but analysis for primary outcome was performed by independent statisticians.		of life, hand grip muscular strength)	for publication. In both groups patients were excluded due to incorrect diagnosis of pancreatitis (N=1 vs N=2), but this would not have had a large impact on the results)	

Randomization: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.

Allocation concealment: refers to the protection (blinding) of the randomization process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomization (performed at a site remote from trial location). Inadequate procedures are all procedures based on inadequate randomization procedures or open allocation schedules..

Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments, but this should not affect the risk of bias judgement. Blinding of those assessing and collecting outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment or data collection (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is usually not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary. Finally, data analysts should be blinded to patient assignment to prevents that knowledge of patient assignment influences data analysis.

Lost to follow-up: If the percentage of patients lost to follow-up or the percentage of missing outcome data is large, or differs between treatment groups, or the reasons for loss to follow-up or missing outcome data differ between treatment groups, bias is likely unless the proportion of missing outcomes compared with observed event risk is not enough to have an important impact on the intervention effect estimate or appropriate imputation methods have been used.

Selective outcome reporting: Results of all predefined outcome measures should be reported; if the protocol is available (in publication or trial registry), then outcomes in the protocol and published report can be compared; if not, outcomes listed in the methods section of an article can be compared with those whose results are reported.

Other biases: Problems may include: a potential source of bias related to the specific study design used (e.g. lead-time bias or survivor bias); trial stopped early due to some data-dependent process (including formal stopping rules); relevant baseline imbalance between intervention groups; claims of fraudulent behavior; deviations from intention-to-treat (ITT) analysis; (the role of the) funding body (see also downgrading due to industry funding https://kennisinstituut.viadesk.com/do/document?id=1607796-646f63756d656e74). Note: The principles of an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

Overall judgement of risk of bias per study and per outcome measure, including predicted direction of bias (e.g. favors experimental, or favors comparator). Note: the decision to downgrade the certainty of the evidence for a particular outcome measure is taken based on the body of evidence, i.e. considering potential bias and its impact on the certainty of the evidence in all included studies reporting on the outcome.

Table of excluded studies

Reference	Reason for exclusion
Bakker OJ, van Santvoort HC, van Brunschot S, Ahmed Ali U, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Brink MA, Dejong CH, van Geenen EJ, van Goor H, Heisterkamp J, Houdijk AP, Jansen JM, Karsten TM, Manusama ER, Nieuwenhuijs VB, van Ramshorst B, Schaapherder AF, van der Schelling GP, Spanier MB, Tan A,	Study protocol

Vecht J, Weusten BL, Witteman BJ, Akkermans LM, Gooszen HG; Dutch Pancreatitis Study Group. Pancreatitis, very early compared with normal start of enteral feeding (PYTHON trial): design and rationale of a randomised controlled multicenter trial. Trials. 2011 Mar 10;12:73. doi: 10.1186/1745-6215-12-73. PMID: 21392395; PMCID: PMC3068962.	
Stimac D, Poropat G, Hauser G, Licul V, Franjic N, Valkovic Zujic P, Milic S. Early nasojejunal tube feeding versus nil-by-mouth in acute pancreatitis: A randomized clinical trial. Pancreatology. 2016 Jul-Aug;16(4):523-8. doi: 10.1016/j.pan.2016.04.003. Epub 2016 Apr 13. PMID: 27107634.	Wrong comparison: control group nil-by-mouth and in both groups an oral diet was gradually instituted, starting with clear liquids on the third day of the protocol
Petrov MS, McIlroy K, Grayson L, Phillips AR, Windsor JA. Early nasogastric tube feeding versus nil per os in mild to moderate acute pancreatitis: a randomized controlled trial. Clin Nutr. 2013 Oct;32(5):697-703. doi: 10.1016/j.clnu.2012.12.011. Epub 2012 Dec 31. PMID: 23340042.	Wrong comparison: control group was on an nil-by-mouth-regimen until the decision of the treating teams to introduce oral feeding.
Ma J, Pendharkar SA, O'Grady G, Windsor JA, Petrov MS. Effect of Nasogastric Tube Feeding vs Nil per Os on Dysmotility in Acute Pancreatitis: Results of a Randomized Controlled Trial. Nutr Clin Pract. 2016 Feb;31(1):99-104. doi: 10.1177/0884533615603967. Epub 2015 Sep 4. PMID: 26341916.	Wrong outcomes
Liu Y, Wan Z, Liao D. Efficacy of enteral nutrition for patients with acute pancreatitis: A systematic review and meta-analysis of 17 studies. Exp Ther Med. 2023 Mar 13;25(4):184. doi: 10.3892/etm.2023.11883. PMID: 37021072; PMCID: PMC10067544.	Wrong timing: early EN (EEN) and delayed EN (DEN) based on different time points (24, 48 and 72 h). No comparison within 24h vs after 72h.
Feng P, He C, Liao G, Chen Y. Early enteral nutrition versus delayed enteral nutrition in acute pancreatitis: A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2017 Nov;96(46):e8648. doi: 10.1097/MD.0000000000008648. PMID: 29145291; PMCID: PMC5704836.	Wrong timing: EEN within 48h versus DEN beyond 48h. Included in this review: Petrov (2013), Bakker (2014); Stimac (2017)
Qi D, Yu B, Huang J, Peng M. Meta-Analysis of Early Enteral Nutrition Provided Within 24 Hours of Admission on Clinical Outcomes in Acute Pancreatitis. JPEN J Parenter Enteral Nutr. 2018 Sep;42(7):1139-1147. doi: 10.1002/jpen.1139. Epub 2018 Jan 26. PMID: 29377204.	No comparison: EEN within 24h.
Li X, Ma F, Jia K. Early enteral nutrition within 24 hours or between 24 and 72 hours for acute pancreatitis: evidence based on 12 RCTs. Med Sci Monit. 2014 Nov 17;20:2327-35. doi: 10.12659/MSM.892770. PMID: 25399541; PMCID: PMC4247233.	Wrong timing: EEN within 24h or between 24h and 72h.
Song J, Zhong Y, Lu X, Kang X, Wang Y, Guo W, Liu J, Yang Y, Pei L. Enteral nutrition provided within 48 hours after admission in severe acute pancreatitis: A systematic review and meta-analysis. Medicine (Baltimore). 2018 Aug;97(34):e11871. doi: 10.1097/MD.0000000000011871. PMID: 30142782; PMCID: PMC6112989.	Wrong timing: within 48 hours or after 48 hours. Included in review: Bakker (2014) and Stimac (2016)
Li JY, Yu T, Chen GC, Yuan YH, Zhong W, Zhao LN, Chen QK. Enteral nutrition within 48 hours of admission improves clinical outcomes of acute pancreatitis by reducing complications: a meta-analysis. PLoS One. 2013 Jun	Wrong timing: Enteral nutrition (EN) initiated within 48 hours of admission and controlled by total parenteral nutrition (TPN) or EN

6;8(6):e64926. doi: 10.1371/journal.pone.0064926. PMID: 23762266; PMCID: PMC3675100.	outside 48 hours. Some studies looked within 24 hours but did not compare to ad libitum/late nutrition.
Kunpeng P, Tianfeng H, Wenyan X, Yang Z, Min Y. Enteral nutrition for severe acute pancreatitis within 48 hours after admission: a meta-analysis. Chinese Journal of Evidence-Based Medicine, 2019, 19(6): 687-693. doi: 10.7507/1672-2531.201811062	Wrong language
Petrov MS, Pylypchuk RD, Uchugina AF. A systematic review on the timing of artificial nutrition in acute pancreatitis. Br J Nutr. 2009 Mar;101(6):787-93. doi: 10.1017/S0007114508123443. Epub 2008 Nov 19. PMID: 19017421.	Wrong timing and comparison: compared enteral versus parenteral nutrition and <48h>
Bakker OJ, van Brunschot S, Farre A, Johnson CD, Kalfarentzos F, Louie BE, Oláh A, O'Keefe SJ, Petrov MS, Powell JJ, Besselink MG, van Santvoort HC, Rovers MM, Gooszen HG. Timing of enteral nutrition in acute pancreatitis: meta-analysis of individuals using a single-arm of randomised trials. Pancreatology. 2014 Sep-Oct;14(5):340-6. doi: 10.1016/j.pan.2014.07.008. Epub 2014 Jul 23. PMID: 25128270.	Wrong timing: starting EN within 24h after hospital admission, compared with after 24h
Sun JK, Li WQ, Ke L, Tong ZH, Ni HB, Li G, Zhang LY, Nie Y, Wang XY, Ye XH, Li N, Li JS. Early enteral nutrition prevents intra-abdominal hypertension and reduces the severity of severe acute pancreatitis compared with delayed enteral nutrition: a prospective pilot study. World J Surg. 2013 Sep;37(9):2053-60. doi: 10.1007/s00268-013-2087-5. PMID: 23674254.	Wrong timing: Enteral nutrition (EN) was started within 48h after admission in the EEN group and from the 8th day in the delayed enteral nutrition (DEN) group.
Jin Z, Wang Z, Wang J. Early Enteral Nutrition Prevent Acute Pancreatitis From Deteriorating in Obese Patients. J Clin Gastroenterol. 2020 Feb;54(2):184-191. doi: 10.1097/MCG.0000000000001117. PMID: 30106837.	Wrong timing: EEN within 48 hours vs DEN after 48 hours.
Liang XY, Wu XA, Tian Y, Gao H, Chen JJ, Feng QX. Effects of Early Versus Delayed Feeding in Patients With Acute Pancreatitis: A Systematic Review and Meta-analysis. J Clin Gastroenterol. 2024 May-Jun 01;58(5):522-530. doi: 10.1097/MCG.0000000000001886. Epub 2023 Jul 10. PMID: 37428071.	Definition of interventions and comparison very broad: studies comparing different timing of refeeding were included, but also studies initiating nutrition when patients 'felt hungry' or when 'bowel sounds are present'
Yao Q, Liu P, Peng S, Xu X, Wu Y. Effects of immediate or early oral feeding on acute pancreatitis: A systematic review and meta-analysis. Pancreatology. 2022 Mar;22(2):175-184. doi: 10.1016/j.pan.2021.11.009. Epub 2021 Dec 1. PMID: 34876385.	No details on timing in hours.
Vaughn VM, Shuster D, Rogers MAM, Mann J, Conte ML, Saint S, Chopra V. Early Versus Delayed Feeding in Patients With Acute Pancreatitis: A Systematic Review. Ann Intern Med. 2017 Jun 20;166(12):883-892. doi: 10.7326/M16-2533. Epub 2017 May 16. PMID: 28505667.	Wrong timing: early versus delayed feeding (≤48 vs >48 hours after hospitalization).
Sharma M, Choudhary V, Padwal U, Gupta SK, Sharma R. Immediate oral refeeding in patients with mild and moderate acute pancreatitis. Journal of Cardiovascular Disease Research. 2023.Volume 14, Issue 2, pp. 2083-2087.	Full text not available.
Talebi S, Zeraattalab-Motlagh S, Vajdi M, Nielsen SM, Talebi A, Ghavami A, Moradi S, Sadeghi E, Ranjbar M, Habibi S, Sadeghi S, Mohammadi H. Early vs delayed enteral	Umbrella review

nutrition or parenteral nutrition in hospitalized patients: An umbrella review of systematic reviews and meta-analyses of randomized trials. Nutr Clin Pract. 2023 Jun;38(3):564-579. doi: 10.1002/ncp.10976. Epub 2023 Mar 12. PMID: 36906848.	
Ramírez-Maldonado E, López Gordo S, Pueyo EM, Sánchez-García A, Mayol S, González S, Elvira J, Memba R, Fondevila C, Jorba R. Immediate Oral Refeeding in Patients With Mild and Moderate Acute Pancreatitis: A Multicenter, Randomized Controlled Trial (PADI trial). Ann Surg. 2021 Aug 1;274(2):255-263. doi: 10.1097/SLA.0000000000004596. PMID: 33196485.	Wrong comparison: IORF group (low-fat-solid diet initiated immediately after hospital admission) vs CORF group (progressive oral diet was restarted when clinical and laboratory parameters had improved)
Khan S, Ranjha WA, Tariq H, Nawaz H. Efficacy of early oral refeeding in patients of mild acute pancreatitis. Pak J Med Sci. 2017 Jul-Aug;33(4):899-902. doi: 10.12669/pjms.334.12338. PMID: 29067062; PMCID: PMC5648961.	Wrong timing: either before or after 12h.
Li J, Xue GJ, Liu YL, Javed MA, Zhao XL, Wan MH, Chen GY, Altaf K, Huang W, Tang WF. Early oral refeeding wisdom in patients with mild acute pancreatitis. Pancreas. 2013 Jan;42(1):88-91. doi: 10.1097/MPA.0b013e3182575fb5. PMID: 22836861.	Intervention/comparison not based on timing but compared EORF (started oral feeding once they subjectively felt hungry) vs patients receiving routine oral refeeding (RORF)
Patil PG, Lamani Y. International Journal of Current Pharmaceutical Review and Research. 2025. Volume 17, Issue 6, pp. 610-614	Wrong timing: EEN within 48 hours vs NPO for 72 hours. 80% of EEN group received nutrition within 1 day but no subanalyses were performed.
Horibe M, Nishizawa T, Suzuki H, Minami K, Yahagi N, Iwasaki E, Kanai T. Timing of oral refeeding in acute pancreatitis: A systematic review and meta-analysis. United European Gastroenterol J. 2016 Dec;4(6):725-732. doi: 10.1177/2050640615612368. Epub 2015 Oct 13. PMID: 28408989; PMCID: PMC5386222.	Intervention/comparison not based on timing but early vs standard.
Guo QH, Tian XY, Qin YL, Han XT, Wang W. Immediate enteral nutrition can accelerate recovery and be safe in mild acute pancreatitis: A meta-analysis of randomized controlled trials. Heliyon. 2022 Feb 1;8(2):e08852. doi: 10.1016/j.heliyon.2022.e08852. PMID: 35198753; PMCID: PMC8844690.	Wrong comparison: Enteral nutrition initiated immediately after admission vs Enteral nutrition after pain relief or bowel sound after admission or parenteral nutrition.
Chen S, Xiong G. Wu S. Chinese Journal of Gastroenterology. 2010. Volume 15, Issue 10, pp. 595-599	Wrong language
Sun JK, Mu XW, Li WQ, Tong ZH, Li J, Zheng SY. Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. World J Gastroenterol. 2013 Feb 14;19(6):917-22. doi: 10.3748/wjg.v19.i6.917. PMID: 23431120; PMCID: PMC3574890.	Wrong timing: Enteral nutrition was started within 48 h in the EEN group and after the 8th day in the DEN group
Lozada-Hernández EE, Barrón-González O, Vázquez-Romero S, Cano-Rosas M, Apolinar-Jimenez E. Non-inferiority comparative clinical trial between early oral REFEEDING and usual oral REFEEDING in predicted mild acute biliary pancreatitis. BMC Gastroenterol. 2020 Jul 16;20(1):228. doi: 10.1186/s12876-020-01363-3. PMID: 32677891; PMCID: PMC7364543.	Wrong timing: in the Early oral refeeding 16-24h after admission; in the usual oral refeeding 25-72h after admission
Eckerwall GE, Tingstedt BB, Bergenzaun PE, Andersson RG. Immediate oral feeding in patients with mild acute	Intervention/comparison not based on timing/hours but when tolerated

pancreatitis is safe and may accelerate recovery--a randomized clinical study. Clin Nutr. 2007 Dec;26(6):758-63. doi: 10.1016/j.clnu.2007.04.007. Epub 2007 Aug 24. PMID: 17719703.	
Esmer D, Rivera-Villalobos O, Hernández-Sierra JF, Valencia-Sánchez LD, Sánchez M. Immediate feeding tolerance in patients with mild acute biliary pancreatitis. Cir Cir. 2021;89(2):243-247. English. doi: 10.24875/CIRU.19001724. PMID: 33784280.	Wrong timing: Immediate oral feeding (8h after the start of management) vs early feeding (48h) in patients with mild acute biliary pancreatitis
Zhang J, Zhu S, Tan D, Ma A, Yang Y, Xu J. A meta-analysis of early oral refeeding and quickly increased diet for patients with mild acute pancreatitis. Saudi J Gastroenterol. 2019 Jan-Feb;25(1):14-19. doi: 10.4103/sjg.SJG_240_18. PMID: 30226482; PMCID: PMC6373213.	Oral feeding time not based on timing.
Márta K, Farkas N, Szabó I, Illés A, Vincze Á, Pár G, Sarlós P, Bajor J, Szűcs Á, Czimmer J, Mosztbacher D, Párniczky A, Szemes K, Pécsi D, Hegyi P. Meta-Analysis of Early Nutrition: The Benefits of Enteral Feeding Compared to a Nil Per Os Diet Not Only in Severe, but Also in Mild and Moderate Acute Pancreatitis. Int J Mol Sci. 2016 Oct 20;17(10):1691. doi: 10.3390/ijms17101691. PMID: 27775609; PMCID: PMC5085723.	Intervention/comparison not based on timing/hours Enteral nutrition vs Nil per os diet (NPO)

Literature search strategy

Zoekstrategie Embase.com 22 juli 2025

No.	*Query*	*Results*
#1	'pancreas necrosis'/exp OR 'acute pancreatitis'/exp OR 'acute hemorrhagic pancreatitis'/exp OR (('pancreatitis'/exp OR pancreatit*:ti,ab,kw OR ((pancrea* NEAR/3 inflammation*):ti,ab,kw)) AND ('necrosis'/de OR acut*:ti,ab,kw OR necroti*:ti,ab,kw OR necros*:ti,ab,kw))	76239
#2	'nutrition'/exp OR 'diet therapy'/exp OR 'artificial feeding'/exp OR 'malnutrition'/exp OR (((calor* OR energ* OR feed OR food* OR meal*) NEAR/3 (intake* OR consumption* OR ingestion* OR uptak* OR support*)):ti,ab,kw) OR (((enteral* OR enteric* OR intragastric* OR intestinal* OR intraintestinal* OR tube* OR method* OR oral*) NEAR/3 (feed OR food*)):ti,ab,kw) OR ((parenteral* NEAR/3 (alimentation* OR feed OR hyperalimentation* OR food* OR intak* OR uptak*)):ti,ab,kw) OR diet*:ti,ab,kw OR nutrit*:ti,ab,kw OR feeding*:ti,ab,kw OR malnutrit*:ti,ab,kw	3936905
#3	#1 AND #2	11951
#4	#3 AND [2005-2025]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'clinical trial':dtype) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	5350
#5	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta	1141135

	analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	
#6	'randomized controlled trial'/exp OR (((pragmatic OR practical) NEAR/1 'clinical trial'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEXT/3 trial):ti,ab) OR rct:ti OR randomly*:ti,ab OR randomi*:ti,ab OR 'random* control*':ti,ab	2191996
#7	#4 AND #5 - SR	469
#8	#4 AND #6 NOT #7 - RCT	381
#9	#7 OR #8 - Totaal	850

Zoekstrategie Ovid/Medline 22 juli 2025

#	Searches	Results
1	exp Pancreatitis, Acute Hemorrhagic/ or exp Pancreatitis, Acute Necrotizing/ or ((exp Pancreatitis/ or pancreatit*.ti,ab,kf. or (pancrea* adj3 inflammation*).ti,ab,kf.) and (exp Acute Disease/ or Necrosis/ or acut*.ti,ab,kf. or necroti*.ti,ab,kf. or necros*.ti,ab,kf.))	43505
2	exp Feeding Methods/ or exp Nutrition Therapy/ or exp Parenteral Nutrition Solutions/ or exp "Diet, Food, and Nutrition"/ or exp Malnutrition/ or ((calor* or energ* or feed or food* or meal*) adj3 (intake* or consumption* or ingestion* or uptak* or support*)).ti,ab,kf. or ((enteral* or enteric* or intragastric* or intestinal* or intraintestinal* or tube* or method* or oral*) adj3 (feed or food*)).ti,ab,kf. or (parenteral* adj3 (alimentation* or feed or hyperalimentation* or food* or intak* or uptak*)).ti,ab,kf. or diet*.ti,ab,kf. or nutrit*.ti,ab,kf. or feeding*.ti,ab,kf. or malnutrit*.ti,ab,kf.	2911229
3	1 and 2	3654
4	limit 3 to yr="2005 -Current"	2336

5	4 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	1950
6	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	848501
7	exp randomized controlled trial/ or randomi*.ti,ab. or rct?.ti,ab. or randomly.ti,ab. or "random* control*".ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab.	1451145
8	5 and 6 - SR	180
9	(5 and 7) not 8 - RCT	189
10	8 or 9 - Totaal	369

Module 5. Pijnbehandeling bij acute pancreatitis

Introduction (English)

Abdominal pain is the defining symptom of acute pancreatitis (AP) and is often severe at presentation, necessitating rapid and effective analgesia to prevent progression to chronic pain. Despite this, pain management remains poorly standardized and largely guided by the WHO analgesic ladder due to lack of substantial evidence. As a result, there is variation in the diagnosis and treatment of pain in AP, leading to practice variation and thus under- or overtreatment of pain.

Opioids are widely used because of their strong and rapid analgesic effects, but their role remains controversial. While effective in reducing pain, they are associated with clinically relevant adverse effects, including nausea, vomiting, ileus, and respiratory depression, which may further complicate AP. In addition, concerns about sphincter of Oddi spasm, as well as risks of tolerance and dependence, limit their suitability. Although opioids provide effective short-term analgesia, their overall benefit in AP is uncertain given their side effect profile and lack of clear superiority over the use of NSAIDs.

Search and select

A systematic review of the literature was performed to answer the following question(s):
What are the (un)beneficial effects of direct opioids in comparison to NSAIDs in patients with acute pancreatitis?

Table 1. PICO

Patients	Adults with acute pancreatitis
Intervention	Opioids
Control	NSAIDs
Outcomes	Mortality, Comprehensive complication index, New onset organ failure, Length of hospital stay, Quality of life, Number of invasive interventions (defined as endoscopic, percutaneous or surgical interventions), Pain (VAS score), need for rescue medication
Other selection criteria	Study design: systematic reviews and randomized controlled trials

Relevant outcome measures

The guideline panel considered length of hospital stay, quality of life, pain (VAS score) and need for rescue medication as **critical** outcome measures for decision making; and mortality, comprehensive complication index, new onset organ failure, number of invasive interventions (defined as endoscopic, percutaneous or surgical interventions) as **important** outcome measures for decision making.

The guideline panel defined the outcome measures as follows:

- Mortality, defined as mortality during index admission
- Number of invasive interventions, defined as endoscopic, percutaneous or surgical interventions
- Pain (VAS score) 24 hours after baseline

A priori, the guideline panel did not define the other outcome measures listed above but used the definitions used in the studies.

The guideline panel defined the following thresholds for minimal clinically important differences:

- Mortality: a relative risk of ≤ 0.91 or ≥ 1.10;
- Other dichotomous outcome measures: a relative risk of ≤ 0.80 or ≥ 1.25;
- Continuous outcome measures: 0.5 x median baseline standard deviation (SD) or 0.5 x standardized mean difference (SMD).

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2005 to the 26th of August 2025 for systematic reviews and RCTs. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from two primary search concepts: (1) acute pancreatitis; (2) direct opioids. Duplicates were removed using EndNote software. After deduplication a total of 194 records were imported for title/abstract screening.

Initially, seven studies were selected based on title and abstract screening. After reading the full text, five studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and two studies were included

Summary of literature

Description of studies

A total of two studies were included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

The systematic literature review of Cai (2021) searched Ovid Medline (PubMed), EMBASE, Science Citation Index Expanded, and Cochrane Library up to June 23, 2021. Inclusion criteria for eligible studies were: (1) RCTs carried out in patients with AP; (2) treatment with opioids, NSAIDs, systemic, or epidural administration of local anaesthetics for abdominal pain; and (3) include at least one outcome measure for analysis. Non-RCTs, retrospective studies, reviews, abstracts, case reports/series, editorials, expert opinions, and non-English publications were excluded. This resulted in four studies that compared opioids versus NSAIDs for the need for rescue analgesia. The primary outcome was the number of patients requiring rescue analgesia beyond the analgesic being tested during the observation time of the trial. Secondary outcomes included change of pain score, all complications, mortality, length of hospital stay, and adverse event rate, but not all these secondary outcomes were measured in the comparison groups opioids versus NSAIDs.

In the single-center, double-blind, 1:1 allocated, parallel-group, randomized controlled, superiority trial of Saini (2024), acute pancreatitis patients received either intravenous diclofenac or intravenous buprenorphine. Inclusion criteria were (1) age 18–75 years, (2) AP defined according to revised Atlanta classification,2 (3) abdominal pain at the time of recruitment, and (4) presentation within the first 5 days of pain onset. Exclusion criteria were (1) pregnancy, (2) acute kidney injury (AKI) (serum creatinine ≥1.4 mg/dL at presentation2), (3) contraindications to opioids/NSAIDs, (4) ongoing therapy with

opioids/NSAIDs for other reasons, (5) history of coronary artery disease, (6) altered mental status, (7) chronic pancreatitis, and (8) requiring mechanical ventilation.

Table 2. Characteristics of included studies

Study	Participants	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Included in systematic review Cai, 2021						
Peiro, 2008	N at baseline Intervention: 8 Control: 8 Age (mean, SD) Intervention: 55.1 ± 18.8 Control: 54.4 ± 13.5 Sex Intervention: 5 male Control: 3 male	Intervention: Morphine (1%, 10mg/4h s.c.) Control: Metamizole (2g/8h, i.v. for 3min)	48h observation time	Pain assessment: VAS (0-100); baseline and every 4h. Rescue analgesia: Pethidine Outcome measures: Pain free within 24 h (<15mm VAS)		Moderate/high risk of bias due to: Low Jadad score in SR, but no detailed information about randomization, blinding, drop-out, allocation concealment..
Gülen, 2016	N at baseline Intervention: 30 Control: 60 (30 paracetamol + 30 dexketoprofen) Age (mean, SD) 53.5 ± 13.3 Sex 53 male	Intervention: Tramadol (1 mg/kg in 100ml saline, i.v., for 4–5min) Control: Paracetamol (1,000mg, i.v., for 4–5min) or dexketoprofen (50 mg/kg, i.v., for 4–5min)	0.5h	Pain assessment: VAS (0–100); baseline and 30min after drug given. Rescue analgesia: Morphine Outcome measures: Pain relief at 30 min; Need for rescue analgesia		Moderate/high risk of bias due to: Moderate Jadad score in SR, but no detailed information about randomization, blinding, drop-out, allocation concealment.

Mahapatra, 2019	N at baseline Intervention: 24 Control: 26 Age (mean, SD) Intervention: 41.3 (11.8) Control: 35.1 (11.8) Sex Intervention: 12 male Control: 12 male	Intervention: Pentazocine (30mg, Q8h, i.v., for 24 h) Control: Diclofenac (75mg, Q8h, i.v., for 24 h)	40h	<u>Pain assessment</u>: N.R. <u>Rescue analgesia</u>: Fentanyl PCIA <u>Outcome measures</u>: Dose of rescue analgesic; Pain free period; Total number of demands of the rescue analgesic		High risk of bias due to: Moderate Jadad score in SR, but no detailed information about randomization, blinding, drop-out, allocation concealment and outcome measures of interest.
Kumar, 2020	N at baseline Intervention: 20 Control: 21 Age (mean, SD) Intervention: 46.8 ± 5.6 Control: 48 ± 12.8 Sex Intervention: 14 male Control: 13 male	Intervention: Diclofenac (1 mg/kg, i.v., over 5min twice daily) Control: Tramadol (1 mg/kg, i.v., over 5min twice daily)	168h	<u>Pain assessment</u>: VAS (0–100); assessed 1, 3, 6, 12 and 24 h after drug given, then every 6 h <u>Rescue analgesia</u>: Morphine (0.06 mg/kg) after the first 1 h then (0.03 mg/kg) after another 30min <u>Outcome measures</u>: VAS after 1 h of drug administration; Need for rescue analgesia		Moderate/high risk of bias due to: High Jadad score in SR, but no detailed information about randomization, blinding, drop-out, allocation concealment.
Individual studies						

Saini, 2024	N at baseline Intervention: 24 Control: 24 Age (mean, range) Intervention: 40 (30–50.75) Control: 34 (26.75–43.25) Sex Intervention: 14 male Control: 13 male	Intervention: Buprenorphine group received 0.3 mg 8-hourly IV for 40 hours. Control: Diclofenac group received 75 mg 8-hourly intravenously (IV) for 40 hours,	The total assessment duration was 72 hours. And a contrast-enhanced computed tomography scan of the abdomen was done at day 5–7 of illness to assess for local complications.	Rescue analgesia: In both groups, rescue analgesic fentanyl was delivered through a PCA pump (CADDLegacy PCA; Infusystem, Rochester Hills, MI). Lock-out interval: 15 min. Primary outcome measure: Dose of rescue fentanyl Secondary outcome measures: Number of total, effective, and ineffective demands Pain free interval Mean VAS (pain scores at baseline and then every 4 h until 72 h from the time of enrollment) Rate of development of organ failure Side effects with buprenorphine: somnolence, vomiting, dizziness, and respiratory depression		Low risk of bias

				Side effects with diclofenac: dyspepsia, gastrointestinal bleeding, and acute kidney injury		

*For further details, see risk of bias table in the appendix

Results

Length of hospital stay (crucial)

Saini (2024) reported on the outcome measure length of hospital stay in days. In the opioid (buprenorphine) group the median hospital stay was reported as 8.0 days (interquartile range (IQR): 8), compared to 5.5 days (IQR: 11) in the NSAID (diclofenac) group.

Cai (2021) did not report on effect on length of hospital stay in the comparison opioids versus NSAIDs.

Quality of life (crucial)

Both Cai (2021) and Saini (2024) did not report on the outcome measure quality of life.

Pain measured as visual analogue scale (VAS) score (crucial)

Saini (2024) reported a mean change in VAS from baseline to 24, 48 and 72 hours. Mean (SD) pain scores at these timepoints are presented in table 3.

Table 3. Mean absolute pain scores at four time points in patients with acute pancreatitis, receiving buprenorphine (opioid) or diclofenac (NSAID) (Saini, 2024).

Intervention	Diclofenac - NSAID (mean (SD))	Buprenorphine – opioid (mean (SD))
Baseline	5.29 (1.78)	5.83 (1.52)
24 hours	4.25 (1.78)	1.46 (1.59)
48 hours	2.96 (2.24)	1.88 (1.68)
72 hours	2.88 (1.65)	1.21 (0.88)

SD: standard deviation.

At 24h from baseline, mean (SD) VAS reduced by 4.38 (1.41) in the opioid (buprenorphine) group, compared to a reduction of 1.04 (2.49) in the NSAID (diclofenac) group. Mean difference in VAS reduction (95%CI) was -3.34 (-4.48 to -2.20). This difference is clinically relevant.

Cai (2021) did not report on effect on pain (VAS) in the comparison opioids versus NSAIDs.

Need for rescue medication (crucial)

Cai (2021) presented results for the need for rescue medication beyond the analgesic being tested during the observation time of the trial. These results were presented based on four studies (n=167) that compared opioids versus NSAIDs. In the opioids group 34/83 (41%) patients needed rescue medication, compared to 42/84 (50%) patients in the NSAIDs group (figure 1). The risk ratio (RR) was 0.94 (95% CI 0.74 to 1.20) in favor of opioids. This difference is not clinically relevant.

Saini (2024) did not report on the outcome measure need for rescue medication.

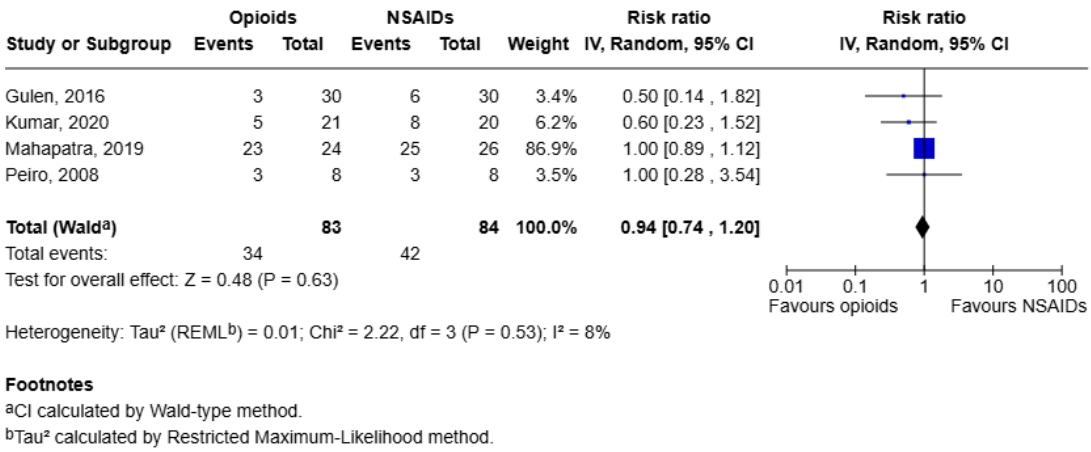

Figure 1: Forest plot on the effect of opioids on need for rescue medication in patients with acute pancreatitis, compared to NSAIDs. Based on data in Cai (2021).

Mortality (important)

Saini (2024) reported on the outcome mortality, defined as all-cause mortality. In both the opioid (buprenorphine) group and the NSAID (diclofenac) group one patient died (4% of 24 in both groups).

Cai (2021) did not report on effect on mortality in the comparison opioids versus NSAIDs.

Comprehensive complication index (important)

Both Cai (2021) and Saini (2024) did not report on the outcome measure comprehensive complication index.

New onset organ failure (important)

Saini (2024) did not report new onset organ failure as a combined outcome measure, but as acute lung injury, acute kidney injury, or cardiovascular failure separately.

In the opioid (buprenorphine) group, the number of acute lung injury was 9/24 (37.5%), compared to 7/24 (29.2%) in the NSAID (diclofenac) group. RR (95%CI) was 1.29 (0.57-2.89), in favor of NSAID. This difference is clinically relevant.

In the opioid (buprenorphine) group, the number of acute kidney injury was 1/24 (4.2%), compared to 2/24 (8.4%) in the NSAID (diclofenac) group. RR (95%CI) was 0.50 (0.05-5.15), in favor of opioid. This difference is clinically relevant.

In the opioid (buprenorphine) group, the number of cardiovascular failure was 1/24 (4.2%), compared to 0/24 (0%) in the NSAID (diclofenac) group. RR (95%CI) was 3.00 (0.13-70.16), in favor of NSAID. This difference is clinically relevant.

Cai (2021) did not report on effect on new onset organ failure in the comparison opioids versus NSAIDs.

Number of invasive interventions (defined as endoscopic, percutaneous or surgical interventions) (important)

Both Cai (2021) and Saini (2024) did not report on the outcome measure number of invasive interventions.

Summary of Findings

Population: Acute pancreatitis
Intervention: Opioids
Comparator: NSAIDs

Outcome	Study results and measurements	Absolute effect estimates NSAIDs Opioids	Certainty of the evidence (Quality of evidence)	Summary
Mortality (important)	Relative risk (CI 95% -) Based on data from 48 participants in 1 studies Follow up 72 hours	**40** per 1000 **40** per 1000 Difference: **0 more per 1000**	**Low** Due to very serious imprecision[1]	Opioids may result in little to no difference in mortality when compared with NSAIDs in patients with acute pancreatitis.
Comprehensive complication index (important)	-	**-**	**No GRADE** (no evidence was found)	No evidence was found regarding the effect of opioids on comprehensive complication index when compared with NSAIDs in patients with acute pancreatitis.
New onset organ failure - acute lung injury (important)	Relative risk: 1.29 (CI 95% 0.57 - 2.89) Based on data from 48 participants in 1 studies Follow up 72 hours	**292** per 1000 **377** per 1000 Difference: **85 more per 1000** (CI 95% 126 fewer - 552 more)	**Very low** Due to very serious imprecision[2]	The evidence is very uncertain about the effect of opioids on new onset organ failure – acute lung injury when compared with NSAIDs in patients with acute pancreatitis.
New onset organ failure - acute kidney injury (important)	Relative risk: 0.5 (CI 95% 0.05 - 5.15) Based on data from 48 participants in 1 studies Follow up 72 hours	**84** per 1000 **42** per 1000 Difference: **42 fewer per 1000** (CI 95% 80 fewer - 349 more)	**Very low** Due to very serious imprecision[3]	The evidence is very uncertain about the effect of opioids on new onset organ failure – acute kidney injury when compared with NSAIDs in patients with acute pancreatitis.
New onset organ failure - cardiovascular failure (important)	Relative risk: 3.0 (CI 95% 0.13 - 70.16) Based on data from 48 participants in 1 studies Follow up 72 hours	**0** per 1000 **42** per 1000 Difference: **42 more per 1000**	**Very low** Due to extremely serious imprecision[4]	The evidence is very uncertain about the effect of opioids on new onset organ failure - cardiovascular failure when compared with NSAIDs in patients with acute pancreatitis.
	Relative risk: 0.94	**500** per 1000 **470** per 1000	**Very low**	The evidence is very uncertain about the effect

Need for rescue medication (critical)	(CI 95% 0.74 - 1.2) Based on data from 167 participants in 4 studies	Difference: **30 fewer per 1000** (CI 95% 130 fewer - 100 more)	Due to serious risk of bias, Due to very serious imprecision[5]	of opioids on need for rescue medication when compared with NSAIDs in patients with acute pancreatitis.
Length of hospital stay (critical)	Based on data from 48 participants in 1 studies Follow up 72 hours	In the opioids group median (IQR) length of hospital stay was 8.0 (8) days, compared to 5.5 (11) days in the NSAID group.	**No GRADE** (data was too limited to perform GRADE-analysis)	Data was too limited regarding the effect of opioids on length of hospital stay when compared with NSAIDs in patients with acute pancreatitis.
Quality of life (critical)	-	-	**No GRADE** (no evidence was found)	No evidence was found regarding the effect of opioids on quality of life when compared with NSAIDs in patients with acute pancreatitis.
Number of invasive interventions (important)	-	-	**No GRADE** (no evidence was found)	No evidence was found regarding the effect of opioids on number of invasive interventions when compared with NSAIDs in patients with acute pancreatitis.
Pain (VAS score) (critical)	Based on data from 48 participants in 1 studies Follow up 72 hours	Mean: **1.04 ± 2.49** Mean: **4.38 ± 1.41** Difference: **3.34 lower** (MD) (CI 95% 4.48 lower - 2.2 lower)	**Low** Due to very serious imprecision[6]	Opioids may result in a higher decrease in pain (VAS score) 24 hours after baseline when compared with NSAIDs in patients with acute pancreatitis.

11. **Imprecision: very serious**. Due to low number of patients (<100), Data of only one study;
12. **Imprecision: extremely serious.** Due to low number of patients (<100), Data of only one study, both limits of the 95% confidence interval overlap with the minimal clinically important difference;
13. **Imprecision: extremely serious.** Due to low number of patients (<100), Data of only one study, both limits of the 95% confidence interval overlap with the minimal clinically important difference;
14. **Imprecision: extremely serious.** Due to low number of patients (<100), Data of only one study, both limits of the 95% confidence interval overlap with the minimal clinically important difference.;
15. **Risk of Bias: serious.** Due to insufficient / lack of blinding; **Imprecision: very serious.** Due to overlap of the lower limit of the 95% confidence interval with the minimal clinically important difference.
16. **Imprecision: very serious.** Due to low number of patients (<100), Data of only one study, both limits of the 95% confidence interval overlap with the minimal clinically important difference;

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor een duidelijk significant beter pijnstillend effect van NSAIDs danwel opioïden voor behandeling van acute pijn in acute pancreatitis. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

In de studies in de literatuursamenvatting zijn verschillende NSAIDs gebruikt, maar de literatuursamenvatting levert geen bewijs welke NSAID het meest effectief is. De verschillende NSAIDs waren diclofenac, metamizol en dexketoprofen. Metamizol en diclofenac worden het vaakst gebruikt.

<u>Kennisvraag 1 :</u>

Wat is bij patiënten met acute pancreatitis en acute pijn de effectiviteit en veiligheid van metamizol (oraal of intraveneus) vergeleken met klassieke NSAID's (diclofenac, naproxen of ibuprofen), ten aanzien van behoefte aan rescue-medicatie, pijnscores en patiënt gerapporteerde uitkomsten zoals tevredenheid en kwaliteit van leven?

P: Patiënt met acute pancreatitis + acute pijn
I: metamizol oraal/iv
C: klassieke NSAIDs (diclofenac, naproxen, ibuprofen) oraal/iv
O: behoefte aan rescue medicatie, pijnscores, patiënttevredenheid/QOL

<u>Kennisvraag 2:</u>

Wat is bij patiënten met acute pancreatitis en acute pijn de effectiviteit van epidurale analgesie ten opzichte van behandeling met paracetamol, al dan niet gecombineerd met NSAID's en/of opioïden, ten aanzien van duur van ziekenhuisopname, behoefte aan rescue-medicatie, pijnscores, patiënttevredenheid en kwaliteit van leven?

P: Patiënt met acute pancreatitis + acute pijn
I: epiduraal analgesie
C: paracetamol + /-NSAIDs +/- opioïden
O: duur ziekenhuisopname, behoefte aan rescue medicatie, pijnscores, patiënttevredenheid/QOL

Implementeren-tabel

Vraag	*Antwoord:* *Kruis aan en licht toe/ beschrijf*		*Toelichting keuze:*
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**X**	**Ongewenste praktijkvariatie**	Sommige klinieken gebruiken opioïden, anderen weer NSAIDS als eerste keuze
		Nieuwe evidentie	
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?		**< 1000**	
		< 5000	
	X	**5000-40.000**	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?	**X**	**Ja**	Verweven met andere interventies, maar losstaand deel.
		Nee	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)			
Zorgverleners (artsen en verpleegkundigen)		Onvoldoende kennis over het gebruik van NSAIDs	Duidelijk behandelplan voor elke patiënt
Patiënt/ cliënt (naasten)		Specifieke contra-indicaties voor NSAIDs. Slechte ervaringen van peers met NSAIDs	Goede pijnstilling, minste bijwerkingen
Sociale context			
Organisatorische context			
Financiële en juridische context			
		A	**B**

I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*	**X**	Patiënt/ cliënt (naaste)	Goede informatie naar de patiënt om een gewogen besluit tussen opioïden en NSAIDs te kunnen nemen
	X	Professional	Goede informatie naar de zorgverlener om een gewogen besluit tussen opioïden en NSAIDs te kunnen nemen
	X	Beroepsvereniging, nl	Aandacht besteden aan acute pijnbehandeling van abdominale pijn bij GI-aandoeningen
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**X**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels)*		Ja *	
	X	Nee	

wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.			

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Literatuur

Cai W, Liu F, Wen Y, Han C, Prasad M, Xia Q, Singh VK, Sutton R, Huang W. Pain Management in Acute Pancreatitis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Front Med (Lausanne). 2021 Dec 17;8:782151. doi: 10.3389/fmed.2021.782151. PMID: 34977084; PMCID: PMC8718672.

Gülen B, Dur A, Serinken M, Karcıoğlu Ö, Sönmez E. Pain treatment in patients with acute pancreatitis: A randomized controlled trial. Turk J Gastroenterol. 2016 Mar;27(2):192-6. doi: 10.5152/tjg.2015.150398. PMID: 27015624.

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Risk of Bias tables

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Saini, 2024	Definitely yes; Reason: single-center, double-blind, 1:1 allocated, parallel-group, randomized-controlled, superiority trial	Definitely yes; Reason: randomization was followed by allocation concealment. This was done with sequentially numbered, opaque, sealed envelopes prepared using computer-generated randomized blocks sequence	Probably yes; Reason: Patients and outcome assessors blinded (blinding of healthcare providers, data collectors and analysts not reported)	Probably yes; Reason: Loss to follow-up was infrequent in intervention and control group.	Definitely yes; Reason: All relevant outcomes were reported	Definitely yes; Reason: No other problems noted	**LOW**

Table of excluded studies

Reference	Reason for exclusion
Nelson AD, Lugo-Fagundo NS, Mahapatra SJ, Cheungpastiporn W, Thongprayoon C, Wijarnpreecha K, Muktesh G, Kochhar R, Garg P, Wallace M, Bi Y. A Systematic Review and Meta-analysis of Opioids vs Nonopioids in Acute Pancreatitis. Gastro Hep Adv. 2022 Feb 3;1(1):83-92. doi: 10.1016/j.gastha.2021.09.006. PMID: 39129925; PMCID: PMC11308224.	6/7 included RCTs were also presented in the SR by Cai (2021) which was of better quality. Search strategy is not reproducable.
Vargas A, Dutta P, Hawa F, Quingalahua E, Marin R, Vilela A, Nix T, Mendoza-Ladd A, Wilcox CM, Chalhoub JM, Machicado JD. Effect of selective COX-2 inhibitors and non-selective non-steroidal anti-inflammatory drugs on severity of acute pancreatitis: A systematic review and meta-analysis. Pancreatology. 2025 Jun;25(4):499-507. doi: 10.1016/j.pan.2025.03.008. Epub 2025 Mar 24. PMID: 40155261.	Subgroup analysis for opioids alone was not published.
Thavanesan N, White S, Lee S, Ratnayake B, Oppong KW, Nayar MK, Sharp L, Drewes AM, Capurso G, De-Madaria E, Siriwardena AK, Windsor JA, Pandanaboyana S. Analgesia in the Initial Management of Acute Pancreatitis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. World J Surg. 2022 Apr;46(4):878-890. doi: 10.1007/s00268-021-06420-w. Epub 2022 Jan 7. PMID: 34994837.	Patient population not clearly described and search strategy not fully available.
Almulhim M, Almulihi QA, Almumtin HS, Alghanim MH, AlAbdulbaqi DA, Almulihi FAA. The Efficacy and Safety of Using Opioids in Acute Pancreatitis: an Update on Systematic Review and Meta-Analysis. Med Arch. 2023;77(4):281-287. doi: 10.5455/medarh.2023.77.281-287. PMID: 37876565; PMCID: PMC10591254.	No subgroup analysis on NSAIDs, children not excluded in the patient population. Search strategy not fully available.
Moazzami B, Mohammadpour Z, Zabala ZE, Chawla S. The Effect of Epidural Analgesia on In-hospital Outcomes in Patients With Acute Pancreatitis: A Systematic Review and Meta-analysis of Randomized Clinical Trials. Pancreas. 2025 Apr 1;54(4):e369-e377. doi: 10.1097/MPA.0000000000002444. PMID: 39626190.	Wrong comparison (sometimes opioids, sometimes NSAIDs in intervention, and in the control)

Literature search strategy

5 ***Zoekstrategie Embase.com 26 augustus 2025***

No.	*Query*	*Results*
#1	'pancreas necrosis'/exp OR 'acute pancreatitis'/exp OR 'acute hemorrhagic pancreatitis'/exp OR (('pancreatitis'/exp OR pancreatit*:ti,ab,kw OR ((pancrea* NEAR/3 inflammation*):ti,ab,kw)) AND ('necrosis'/de OR acut*:ti,ab,kw OR necroti*:ti,ab,kw OR necros*:ti,ab,kw))	76650

#2	'opiate'/exp OR algopan:ti,ab,kw OR biopon:ti,ab,kw OR cofapon:ti,ab,kw OR dropizol:ti,ab,kw OR laudanon:ti,ab,kw OR laudanum:ti,ab,kw OR laudopan:ti,ab,kw OR nepenthe:ti,ab,kw OR omnopon:ti,ab,kw OR opial:ti,ab,kw OR opiat*:ti,ab,kw OR opioid*:ti,ab,kw OR opium*:ti,ab,kw OR opon:ti,ab,kw OR oposal:ti,ab,kw OR pantopon*:ti,ab,kw OR papaveretum:ti,ab,kw OR pavon:ti,ab,kw OR tetrapon:ti,ab,kw	267080
#3	'oxycodone'/exp OR 'abtard':ti,ab,kw OR 'accordeon':ti,ab,kw OR 'alivio':ti,ab,kw OR 'bionine':ti,ab,kw OR 'bionone':ti,ab,kw OR 'bolodorm':ti,ab,kw OR 'broncodal':ti,ab,kw OR 'bucodal':ti,ab,kw OR 'cafacodal':ti,ab,kw OR 'candox':ti,ab,kw OR 'cardanon':ti,ab,kw OR 'carenoxal':ti,ab,kw OR 'carexil':ti,ab,kw OR 'celastymis':ti,ab,kw OR 'codenon':ti,ab,kw OR 'codilek':ti,ab,kw OR 'codix 5':ti,ab,kw OR 'codoxy':ti,ab,kw OR 'col 003':ti,ab,kw OR 'col003':ti,ab,kw OR 'contiroxil':ti,ab,kw OR 'contiroxin':ti,ab,kw OR 'daloxy':ti,ab,kw OR 'dancex':ti,ab,kw OR 'dihydrohydroxycodeinone':ti,ab,kw OR 'dihydrohydroxydodeinone':ti,ab,kw OR 'dihydrone':ti,ab,kw OR 'dinarkon':ti,ab,kw OR 'dolanor':ti,ab,kw OR 'dolocodon':ti,ab,kw OR 'dyxal':ti,ab,kw OR 'endone':ti,ab,kw OR 'enoxy':ti,ab,kw OR 'eubine':ti,ab,kw OR 'eucodal':ti,ab,kw OR 'eucodale':ti,ab,kw OR 'eucodalum':ti,ab,kw OR 'eudin':ti,ab,kw OR 'eukdin':ti,ab,kw OR 'eukodal':ti,ab,kw OR 'eumorphal':ti,ab,kw OR 'eurodamine':ti,ab,kw OR 'eutagen':ti,ab,kw OR 'gl 2907':ti,ab,kw OR 'gl2907':ti,ab,kw OR 'hydrocodal':ti,ab,kw OR 'hydroxycodeinoma':ti,ab,kw OR 'ixyldone':ti,ab,kw OR 'lenocod':ti,ab,kw OR 'leveraxo':ti,ab,kw OR 'longtec':ti,ab,kw OR 'ludonal':ti,ab,kw OR 'lynlor':ti,ab,kw OR 'm-oxy':ti,ab,kw OR 'medicodal':ti,ab,kw OR 'mnk 812':ti,ab,kw OR 'mnk812':ti,ab,kw OR 'narcobasina':ti,ab,kw OR 'narcobasine':ti,ab,kw OR 'narcosin':ti,ab,kw OR 'nargenol':ti,ab,kw OR 'narodal':ti,ab,kw OR 'nsc 19043':ti,ab,kw OR 'nsc19043':ti,ab,kw OR 'nucodan':ti,ab,kw OR 'oksikodon':ti,ab,kw OR 'olbete':ti,ab,kw OR 'onexila':ti,ab,kw OR 'opton':ti,ab,kw OR 'orionox':ti,ab,kw OR 'ossicodone':ti,ab,kw OR 'oxanest':ti,ab,kw OR 'oxaydo':ti,ab,kw OR 'oxecta':ti,ab,kw OR 'oxeltra':ti,ab,kw OR 'oxicodona':ti,ab,kw OR 'oxicone':ti,ab,kw OR 'oxicontin':ti,ab,kw OR 'oxiconum':ti,ab,kw OR 'oxidol*':ti,ab,kw OR 'oxikodon*':ti,ab,kw OR 'oxikon':ti,ab,kw OR 'oxinorm':ti,ab,kw OR 'oxpian':ti,ab,kw OR 'oxy ir':ti,ab,kw OR 'oxyact':ti,ab,kw OR 'oxycan':ti,ab,kw OR 'oxycod':ti,ab,kw OR 'oxycodeinonhydrochloride':ti,ab,kw OR 'oxycodon':ti,ab,kw OR 'oxycodone*':ti,ab,kw OR 'oxycodonhydrochlorid':ti,ab,kw OR 'oxycodyl':ti,ab,kw OR 'oxycone':ti,ab,kw OR 'oxyconica':ti,ab,kw OR 'oxyconicur':ti,ab,kw OR 'oxyconoica':ti,ab,kw OR 'oxycontin*':ti,ab,kw OR 'oxydol*':ti,ab,kw OR 'oxydon':ti,ab,kw OR 'oxydose':ti,ab,kw OR 'oxyfast':ti,ab,kw OR 'oxygerolan':ti,ab,kw OR 'oxygesic':ti,ab,kw OR 'oxyir':ti,ab,kw OR 'oxykodon':ti,ab,kw OR 'oxykon':ti,ab,kw OR 'oxylan':ti,ab,kw OR	28508

	'oxylor':ti,ab,kw OR 'oxyneo':ti,ab,kw OR 'oxynorm':ti,ab,kw OR 'oxynormoro':ti,ab,kw OR 'oxyora':ti,ab,kw OR 'oxypro':ti,ab,kw OR 'oxyratio':ti,ab,kw OR 'oxytina':ti,ab,kw OR 'pancodine':ti,ab,kw OR 'pavinal':ti,ab,kw OR 'percolone':ti,ab,kw OR 'pf 00345439':ti,ab,kw OR 'pf00345439':ti,ab,kw OR 'pronarcin':ti,ab,kw OR 'pti 821':ti,ab,kw OR 'pti821':ti,ab,kw OR 'reltebon':ti,ab,kw OR 'remoxy':ti,ab,kw OR 'renocontin':ti,ab,kw OR 'roxicodone':ti,ab,kw OR 'roxybond':ti,ab,kw OR 'roxycodone':ti,ab,kw OR 'shortec':ti,ab,kw OR 'sinthiodal':ti,ab,kw OR 'stupenal':ti,ab,kw OR 'supeudol':ti,ab,kw OR 'taioma':ti,ab,kw OR 'tebodal':ti,ab,kw OR 'tekodin':ti,ab,kw OR 'thecodin':ti,ab,kw OR 'tk 641':ti,ab,kw OR 'tk641':ti,ab,kw OR 'xancodal':ti,ab,kw OR 'xtampa':ti,ab,kw OR 'xtampza':ti,ab,kw OR 'zarenoxin':ti,ab,kw OR 'zomestine':ti,ab,kw	
#4	'morphine'/exp OR 'anpec':ti,ab,kw OR 'duromorph':ti,ab,kw OR 'epimorph':ti,ab,kw OR 'maracex':ti,ab,kw OR 'miro':ti,ab,kw OR 'morfin*':ti,ab,kw OR 'morphia':ti,ab,kw OR 'morphin':ti,ab,kw OR 'morphine':ti,ab,kw OR 'morphinium':ti,ab,kw OR 'morphium':ti,ab,kw OR 'opso':ti,ab,kw OR 'sendolor':ti,ab,kw OR 'skenan':ti,ab,kw	147630
#5	#2 OR #3 OR #4	357186
#6	#1 AND #5	1179
#7	#6 AND [2005-2025]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'clinical trial':dtype) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	555
#8	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR	1153573

	medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	
#9	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4888660
#10	#7 AND #8 - SR	50
#11	#7 AND #9 NOT #10 - RCT	132
#12	#10 OR #11 - Totaal	182

Zoekstrategie Ovid/Medline 26 augustus 2025

#	Searches	Results
1	exp Pancreatitis, Acute Hemorrhagic/ or exp Pancreatitis, Acute Necrotizing/ or ((exp Pancreatitis/ or pancreatit*.ti,ab,kf. or (pancrea* adj3 inflammation*).ti,ab,kf.) and (exp Acute Disease/ or Necrosis/ or acut*.ti,ab,kf. or necroti*.ti,ab,kf. or necros*.ti,ab,kf.))	43686
2	exp Opiate Alkaloids/ or algopan.ti,ab,kf. or biopon.ti,ab,kf. or cofapon.ti,ab,kf. or dropizol.ti,ab,kf. or laudanon.ti,ab,kf. or laudanum.ti,ab,kf. or laudopan.ti,ab,kf. or nepenthe.ti,ab,kf. or omnopon.ti,ab,kf. or opial.ti,ab,kf. or opiat*.ti,ab,kf. or opioid*.ti,ab,kf. or opium*.ti,ab,kf. or opon.ti,ab,kf. or oposal.ti,ab,kf. or pantopon*.ti,ab,kf. or papaveretum.ti,ab,kf. or pavon.ti,ab,kf. or tetrapon.ti,ab,kf.	210341
3	exp Oxycodone/ or exp Analgesics, Opioid/ or abtard.ti,ab,kf. or accordeon.ti,ab,kf. or alivio.ti,ab,kf. or bionine.ti,ab,kf. or bionone.ti,ab,kf. or bolodorm.ti,ab,kf. or broncodal.ti,ab,kf. or bucodal.ti,ab,kf. or cafacodal.ti,ab,kf. or candox.ti,ab,kf. or cardanon.ti,ab,kf. or carenoxal.ti,ab,kf. or carexil.ti,ab,kf. or celastymis.ti,ab,kf. or codenon.ti,ab,kf. or codilek.ti,ab,kf. or codix 5.ti,ab,kf. or codoxy.ti,ab,kf. or "col 003".ti,ab,kf. or col003.ti,ab,kf. or contiroxil.ti,ab,kf. or contiroxin.ti,ab,kf. or daloxy.ti,ab,kf. or dancex.ti,ab,kf. or dihydrohydroxycodeinone.ti,ab,kf. or dihydrohydroxydodeinone.ti,ab,kf. or dihydrone.ti,ab,kf. or dinarkon.ti,ab,kf. or dolanor.ti,ab,kf. or dolocodon.ti,ab,kf. or dyxal.ti,ab,kf. or endone.ti,ab,kf. or enoxy.ti,ab,kf. or eubine.ti,ab,kf. or eucodal.ti,ab,kf. or eucodale.ti,ab,kf. or eucodalum.ti,ab,kf. or eudin.ti,ab,kf. or eukdin.ti,ab,kf. or eukodal.ti,ab,kf. or eumorphal.ti,ab,kf. or eurodamine.ti,ab,kf. or eutagen.ti,ab,kf. or gl 2907.ti,ab,kf. or gl2907.ti,ab,kf. or hydrocodal.ti,ab,kf. or hydroxycodeinoma.ti,ab,kf. or ixyldone.ti,ab,kf. or lenocod.ti,ab,kf. or leveraxo.ti,ab,kf. or longtec.ti,ab,kf. or ludonal.ti,ab,kf. or lynlor.ti,ab,kf. or m-oxy.ti,ab,kf. or medicodal.ti,ab,kf. or mnk 812.ti,ab,kf. or mnk812.ti,ab,kf. or narcobasina.ti,ab,kf. or narcobasine.ti,ab,kf. or narcosin.ti,ab,kf. or nargenol.ti,ab,kf. or narodal.ti,ab,kf. or nsc	146997

	19043.ti,ab,kf. or nsc19043.ti,ab,kf. or nucodan.ti,ab,kf. or oksikodon.ti,ab,kf. or olbete.ti,ab,kf. or onexila.ti,ab,kf. or opton.ti,ab,kf. or orionox.ti,ab,kf. or ossicodone.ti,ab,kf. or oxanest.ti,ab,kf. or oxaydo.ti,ab,kf. or oxecta.ti,ab,kf. or oxeltra.ti,ab,kf. or oxicodona.ti,ab,kf. or oxicone.ti,ab,kf. or oxicontin.ti,ab,kf. or oxiconum.ti,ab,kf. or oxidol*.ti,ab,kf. or oxikodon*.ti,ab,kf. or oxikon.ti,ab,kf. or oxinorm.ti,ab,kf. or oxpian.ti,ab,kf. or oxy ir.ti,ab,kf. or oxyact.ti,ab,kf. or oxycan.ti,ab,kf. or oxycod.ti,ab,kf. or oxycodeinonhydrochloride.ti,ab,kf. or oxycodon.ti,ab,kf. or oxycodone*.ti,ab,kf. or oxycodonhydrochlorid.ti,ab,kf. or oxycodyl.ti,ab,kf. or oxycone.ti,ab,kf. or oxyconica.ti,ab,kf. or oxyconicur.ti,ab,kf. or oxyconoica.ti,ab,kf. or oxycontin*.ti,ab,kf. or oxydol*.ti,ab,kf. or oxydon.ti,ab,kf. or oxydose.ti,ab,kf. or oxyfast.ti,ab,kf. or oxygerolan.ti,ab,kf. or oxygesic.ti,ab,kf. or oxyir.ti,ab,kf. or oxykodon.ti,ab,kf. or oxykon.ti,ab,kf. or oxylan.ti,ab,kf. or oxylor.ti,ab,kf. or oxyneo.ti,ab,kf. or oxynorm.ti,ab,kf. or oxynormoro.ti,ab,kf. or oxyora.ti,ab,kf. or oxypro.ti,ab,kf. or oxyratio.ti,ab,kf. or oxytina.ti,ab,kf. or pancodine.ti,ab,kf. or pavinal.ti,ab,kf. or percolone.ti,ab,kf. or "pf 00345439".ti,ab,kf. or pf00345439.ti,ab,kf. or pronarcin.ti,ab,kf. or pti 821.ti,ab,kf. or pti821.ti,ab,kf. or reltebon.ti,ab,kf. or remoxy.ti,ab,kf. or renocontin.ti,ab,kf. or roxicodone.ti,ab,kf. or roxybond.ti,ab,kf. or roxycodone.ti,ab,kf. or shortec.ti,ab,kf. or sinthiodal.ti,ab,kf. or stupenal.ti,ab,kf. or supeudol.ti,ab,kf. or taioma.ti,ab,kf. or tebodal.ti,ab,kf. or tekodin.ti,ab,kf. or thecodin.ti,ab,kf. or tk 641.ti,ab,kf. or tk641.ti,ab,kf. or xancodal.ti,ab,kf. or xtampa.ti,ab,kf. or xtampza.ti,ab,kf. or zarenoxin.ti,ab,kf. or zomestine.ti,ab,kf.	
4	exp Morphine/ or anpec.ti,ab,kf. or duromorph.ti,ab,kf. or epimorph.ti,ab,kf. or maracex.ti,ab,kf. or miro.ti,ab,kf. or morfin*.ti,ab,kf. or morphia.ti,ab,kf. or morphin.ti,ab,kf. or morphine.ti,ab,kf. or morphinium.ti,ab,kf. or morphium.ti,ab,kf. or opso.ti,ab,kf. or sendolor.ti,ab,kf. or skenan.ti,ab,kf.	67679
5	2 or 3 or 4	254729
6	1 and 5	351
7	limit 6 to yr="2005 -Current"	232
8	7 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	211
9	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or	853595

	(medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	
10	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2932182
11	8 and 9 - SR	20
12	(8 and 10) not 11 - RCT	47
13	11 or 12 - Totaal	67

Module 6. Antibiotica bij verdenking geïnfecteerde necrotiserende pancreatitis

Introduction (English)

There are no comparative studies investigating which empirical antibiotic therapy should be initiated in patients suspected of having infected pancreatic necrosis. In clinical practice, carbapenems are frequently chosen, despite the importance of a carbapenem-sparing strategy whenever possible to minimize the development of resistance.

Search and select

A systematic review of the literature was performed to answer the following question(s): What are the benefits and harms of carbapenem-based empirical antibiotic treatment in comparison to other broad-spectrum empirical antibiotic treatment in patients with acute necrotizing pancreatitis and suspected or proven infected necrosis?

Table 1. PICO

Patients	Adult patients with acute necrotizing pancreatitis and suspected or proven infected necrosis*
Intervention	Carbapenem-based empirical antibiotic treatment
Control	Other broad-spectrum empirical antibiotic treatment
Outcomes	Mortality, new-onset organ failure, length of hospital stay, comprehensive complication index, quality of life, number of invasive interventions, adverse events and duration of antibiotic treatment
Other selection criteria	Study design: systematic reviews, randomized controlled trials (RCTs) and observational comparative studies, in which analyses were adjusted for confounding If available: subgroup analysis for patients with and without antibiotic pretreatment

*** In a setting with low prevalence of colonization with ESBL-producing Enterobacterales in the general population, similar to estimated *extended spectrum beta-lactamase* (ESBL) colonization prevalence in the Netherlands (<10%, Reuland, 2016)**

Relevant outcome measures

The guideline panel considered all-cause mortality and number of invasive interventions for infected necrosis as **critical** outcome measures for decision making; and new-onset organ failure, length of hospital stay, comprehensive complication index, quality of life, adverse events and duration of antibiotic treatment as **important** outcome measures for decision making.

The guideline panel defined the outcome measures as follows:

- Mortality, defined as all-cause mortality
- Number of invasive interventions for infected necrosis, defined as endoscopic, percutaneous or surgical interventions as (supportive) therapeutic intervention for infected necrosis
- Duration of antibiotic treatment: overall and with carbapenem, for any infection and for infected necrosis

The guideline panel did not define time windows for specified outcomes (e.g. 30-day mortality), nor other outcome measures a priori, but proposed to report time windows and

other outcomes as defined by the study authors and as deemed relevant by guideline panel members.

The guideline panel defined the following thresholds for minimal clinically important differences:

- Mortality: a relative risk of ≤ 0.91 or ≥ 1.10;
- Other dichotomous outcome measures: a relative risk of ≤ 0.80 or ≥ 1.25;
- Continuous outcome measures: 0.5 x median baseline standard deviation (SD) or 0.5 x standardized mean difference (SMD).

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2005 to the 12th of August 2025 for guidelines, systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from two primary search concepts: (1) necrotizing pancreatitis; (2) carbapenem. Duplicates were removed using EndNote software. After deduplication a total of 384 records were imported for title/abstract screening. Initially, one study was selected based on title and abstract screening. After reading the full text, this study was excluded (see the exclusion table under the tab 'Evidence tabellen'), and no study was included.

Summary of literature

The search resulted in one potentially relevant study. Full-text assessment led to its exclusion (see exclusion table), leaving no studies that met the criteria for inclusion in the systematic literature analysis.

Description of studies

n.a.

Results

n.a.

Summary of Findings

n.a.

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvragen:

- Welke definitieve antibiotica dient te worden gekozen bij aangetoonde geinfecteerde pancreasnecrose?
    - In lijn: moeten laag-pathogene micro-organismen die gedetecteerd worden in geïnfecteerde necrose behandeld worden?
      Patients: (confirmed) infected necrotizing pancreatitis
      Intervention: definitive antibiotic treatment strategy targeted against all cultured micro-organisms (e.g. including yeast and enterococci)
      Control: definitive antibiotic treatment strategy targeted against a selection of cultured micro-organisms (e.g. excluding yeast and enterococci)
      Outcome: Additionale pancreas interventies, mortaliteit, gebruik reserve antibiotica, opnameduur.

- Wat is de behandelduur van antibiotica bij patiënten met geïnfecteerde pancreasnecrose zonder drainage?
  PICO
  Patients: infected necrotizing pancreatitis
  Intervention: Gestandaaridseerde/ geprotocolleerde duur antibiotica
  Control: huidige zorg (geen protocol)
  Outcome : Pancreas interventies, mortaliteit, gebruik reserve antibiotica, opnameduur.
- Wat is de behandelduur van antibiotica bij patiënten met geïnfecteerde pancreasnecrose na drainage?
  Patients: infected necrotizing pancreatitis na drainage (percutaan of endoscopisch)
  Intervention: Gestandaaridseerde/ geprotocolleerder duur antibiotica
  Control: huidige zorg (geen protocol)
  Outcome : Additionale pancreas interventies, mortaliteit, gebruik reserve antibiotica, opnameduur.

- Wat is de behandelduur van antibiotica bij patiënten met geïnfecteerde pancreasnecrose na necrosectomie?
  Patients: infected necrotizing pancreatitis na necrosectomie (VARD of endoscopisch)
  Intervention: Gestandaardiseerde/ geprotocolleerder duur antibiotica
  Control: huidige zorg (geen protocol)
  Outcome : Additionale pancreas interventies, mortaliteit, gebruik reserve antibiotica, opnameduur.

- Hoe is optimaal onderscheid te maken tussen een infectie zoals geïnfecteerde pancreasnecrose en een SIRS reactie bij een ernstige pancreatitis? PICO:
  Patients: (suspected infected necrotizing pancreatitis
  Intervention: Diagnostic bundle and/or biomarker
  Control: Current standard (gas bubbles/ clinical criteria)
  Outcome: Infected pancreatic necrosis

- Is er een rol voor FNA voor start empirische therapie om meer kweekgestuurd antibiotica te kunnen starten?

  Patients: (suspected infected necrotizing pancreatitis
  Intervention: FNA based antibiotic therapy
  Control: Current standard (no FNA, empirical therapy in case of suspected infection)
  Outcome: Pancreas interventies, mortaliteit, gebruik reserve antibiotica, opnameduur.

Implementeren-tabel

De implementatietabel brengt in kaart welke factoren de uitvoering van een aanbeveling bevorderen of belemmeren, en welke aanvullende acties nodig zijn voor succesvolle invoering. De adviseur en (cluster)werkgroep vullen de tabel in op basis van gerichte vragen over het onderliggende probleem, relevante randvoorwaarden en mogelijke knelpunten. Op basis hiervan wordt geconcludeerd of een extra implementatie-impuls wenselijk is.

Implementatietabel

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**x**	**Ongewenste praktijkvariatie**	
		Nieuwe evidentie	
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**x**	**< 1000**	
		< 5000	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?	**x**	**Ja**	(Bijna) elk ziekenhuis in Nederland heeft het volgende ingericht: - een A-team dat gericht is op antibiotic stewardship en carbapenem-sparend beleid en daarbij de SWAB richtlijn antibiotic stewardship volgt - een antibioticacommissie dat het antibioticabeleid bepaalt - een antibioticaformularium, de meesten via swabid dat centraal een advies kan sturen
		Nee	

I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)			FMS richtlijn sluit aan bij SWAB antibiotic stewardship en SWAB sepsis richtlijn
Zorgverleners (artsen en verpleegkundigen)		Gewoontes, overtuigingen	"Antibiotic stewardship champions"
Patiënt/ cliënt (naasten)			
Sociale context			
Organisatorische context			Al veel ingericht in Nederland en in ziekenhuizen om carbapenemsparend beleid te voeren Doorvoeren in swabid
Financiële en juridische context			
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
		Patiënt/ cliënt (naaste)	
	x	Professional	MDL artsen, microbiologen, leden van antibioticacommissie en A-team
	x	Beroepsvereniging, nl	NVMDL, NVMM, NVvH, NIV, NVZA
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?		< 1 jaar	
	X	binnen 2-3 jaar	Toelichting: de PIANO-studie loopt nog tot 2026 en resultaten worden verwacht in 2027. Deze uitkomsten zullen

			naar verwachting verdere richting geven aan de implementatie en het bijbehorende implementatieplan.
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*		Ja	
	X	Nee	De aanbeveling sluit aan bij bestaande SWAB-richtlijnen en antibiotic stewardship-principes. Gezien de beperkte onderbouwing door evidence worden aanvullende implementatieactiviteiten momenteel niet noodzakelijk geacht.
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*		Ja *	
	X	Nee	De aanbeveling past binnen bestaande landelijke kaders, waaronder SWAB antibiotic stewardship en sepsisbeleid. Gezien de beperkte omvang en onderbouwing van de aanbeveling wordt plaatsing op de Landelijke Implementatieagenda niet noodzakelijk geacht.

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

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Bijlagen bij module Antibioticabeleid

Risk of Bias tables

Not applicable

Table of excluded studies

Reference	Reason for exclusion

Literature search strategy

Zoekstrategie Embase.com 12 augustus 2025

No.	*Query*	*Results*
#1	'pancreas necrosis'/exp OR 'acute pancreatitis'/exp OR 'acute hemorrhagic pancreatitis'/exp OR (('pancreatitis'/exp OR pancreatit*:ti,ab,kw OR ((pancrea* NEAR/3 inflammation*):ti,ab,kw)) AND ('necrosis'/de OR acut*:ti,ab,kw OR necroti*:ti,ab,kw OR necros*:ti,ab,kw))	76499
#2	'carbapenem'/exp OR 'meropenem'/exp OR 'imipenem'/exp OR 'cilastatin plus imipenem'/exp OR 'ertapenem'/exp OR 'doripenem'/exp OR 'panipenem'/exp OR 'panipenem plus betamipron'/exp OR 'biapenem'/exp OR 'fropenem'/exp OR 'tebipenem'/exp OR 'tebipenem pivoxil'/exp OR 'razupenem'/exp OR 'lenapenem'/exp OR 'sulopenem'/exp OR 'tomopenem'/exp OR 'thienamycin'/exp OR 'carbapenem':ti,ab,kw OR 'ici 194660':ti,ab,kw OR 'mepem':ti,ab,kw OR 'meronem':ti,ab,kw OR 'meropen':ti,ab,kw OR 'meropenem':ti,ab,kw OR 'merrem':ti,ab,kw OR 'sm 7338':ti,ab,kw OR 'sm7338':ti,ab,kw OR 'formiminothienamycin':ti,ab,kw OR 'imipemide':ti,ab,kw OR 'imipenem':ti,ab,kw OR 'mk 0787':ti,ab,kw OR 'mk 787':ti,ab,kw OR 'bacqure':ti,ab,kw OR 'cilapem':ti,ab,kw OR ((cilastatin NEAR/3 imipenem):ti,ab,kw) OR 'ime-cila':ti,ab,kw OR 'imipenem plus cilastatin':ti,ab,kw OR 'imipenem plus cilastatin sodium':ti,ab,kw OR 'mk 797':ti,ab,kw OR 'mk797':ti,ab,kw OR 'pelastin iv':ti,ab,kw OR 'prepenem':ti,ab,kw OR 'primaxin':ti,ab,kw OR 'tenacid':ti,ab,kw OR 'tienam':ti,ab,kw OR 'tienem':ti,ab,kw OR 'xerxes iv':ti,ab,kw OR 'zienam':ti,ab,kw OR 'ertapenem':ti,ab,kw OR 'invanoz':ti,ab,kw OR 'invanz':ti,ab,kw OR 'l 749345':ti,ab,kw OR 'l749345':ti,ab,kw OR 'mk 0826':ti,ab,kw OR 'mk 826':ti,ab,kw OR 'mk0826':ti,ab,kw OR 'mk826':ti,ab,kw OR 'zd 4433':ti,ab,kw OR 'zd4433':ti,ab,kw OR 'doribax':ti,ab,kw OR 'doripenem':ti,ab,kw OR 'finibax':ti,ab,kw OR 's 4661':ti,ab,kw OR 's4661':ti,ab,kw OR 'cs 533':ti,ab,kw OR 'cs533':ti,ab,kw OR 'panipenem':ti,ab,kw OR 'rs 533':ti,ab,kw OR 'rs533':ti,ab,kw OR ((betamipron NEAR/3 panipenem):ti,ab,kw) OR 'carbenin':ti,ab,kw OR 'cs 976':ti,ab,kw OR 'cs976':ti,ab,kw OR 'biapenem':ti,ab,kw OR 'cl 186815':ti,ab,kw OR 'cl186815':ti,ab,kw OR 'cli 86815':ti,ab,kw OR 'cli86815':ti,ab,kw OR 'l 627':ti,ab,kw OR 'l627':ti,ab,kw OR	120417

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#3	#1 AND #2	1280
#4	#3 AND [2005-2025]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'clinical trial':dtype) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	793
#5	'practice guideline'/exp OR 'standard'/de OR guideline*:ti,kw OR cpg:ti,kw OR consensus*:ti,kw	1260396
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	comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	
#7	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4876934
#8	'major clinical study'/de OR 'clinical study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR 'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR	18893150

	cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#9	#4 AND #5 - Guidelines	56
#10	#4 AND #6 NOT #9 - SR	53
#11	#4 AND #7 NOT (#9 OR #10) - RCT	100
#12	#4 AND #8 NOT (#9 OR #10 OR #11) - Observationeel	167
#13	#9 OR #10 OR #11 OR #12 - Totaal	376

Zoekstrategie Ovid/Medline 12 augustus 2025

#	Searches	Results
1	exp Pancreatitis, Acute Hemorrhagic/ or exp Pancreatitis, Acute Necrotizing/ or ((exp Pancreatitis/ or pancreatit*.ti,ab,kf. or (pancrea* adj3 inflammation*).ti,ab,kf.) and (exp Acute Disease/ or Necrosis/ or acut*.ti,ab,kf. or necroti*.ti,ab,kf. or necros*.ti,ab,kf.))	43648
2	exp Carbapenems/ or exp Meropenem/ or exp Imipenem/ or exp Cilastatin, Imipenem Drug Combination/ or exp Ertapenem/ or exp Doripenem/ or exp Thienamycins/ or 'carbapenem'.ti,ab,kf. or 'ici 194660'.ti,ab,kf. or 'mepem'.ti,ab,kf. or 'meronem'.ti,ab,kf. or 'meropen'.ti,ab,kf. or 'meropenem'.ti,ab,kf. or 'merrem'.ti,ab,kf. or 'sm 7338'.ti,ab,kf. or 'sm7338'.ti,ab,kf. or 'formiminothienamycin'.ti,ab,kf. or 'imipemide'.ti,ab,kf. or 'imipenem'.ti,ab,kf. or 'mk 0787'.ti,ab,kf. or 'mk 787'.ti,ab,kf. or 'bacqure'.ti,ab,kf. or 'cilapem'.ti,ab,kf. or (cilastatin adj3 imipenem).ti,ab,kf. or 'ime-cila'.ti,ab,kf. or 'imipenem plus cilastatin'.ti,ab,kf. or 'imipenem plus cilastatin sodium'.ti,ab,kf. or 'mk 797'.ti,ab,kf. or 'mk797'.ti,ab,kf. or 'pelastin iv'.ti,ab,kf. or 'prepenem'.ti,ab,kf. or 'primaxin'.ti,ab,kf. or 'tenacid'.ti,ab,kf. or 'tienam'.ti,ab,kf. or 'tienem'.ti,ab,kf. or 'xerxes iv'.ti,ab,kf. or 'zienam'.ti,ab,kf. or 'ertapenem'.ti,ab,kf. or 'invanoz'.ti,ab,kf. or 'invanz'.ti,ab,kf. or 'l 749345'.ti,ab,kf. or 'l749345'.ti,ab,kf. or 'mk 0826'.ti,ab,kf. or 'mk 826'.ti,ab,kf. or 'mk0826'.ti,ab,kf. or 'mk826'.ti,ab,kf. or 'zd 4433'.ti,ab,kf. or 'zd4433'.ti,ab,kf. or 'doribax'.ti,ab,kf. or 'doripenem'.ti,ab,kf. or 'finibax'.ti,ab,kf. or 's 4661'.ti,ab,kf. or 's4661'.ti,ab,kf. or 'cs 533'.ti,ab,kf. or 'cs533'.ti,ab,kf. or 'panipenem'.ti,ab,kf. or 'rs 533'.ti,ab,kf. or 'rs533'.ti,ab,kf. or (betamipron adj3 panipenem).ti,ab,kf. or 'carbenin'.ti,ab,kf. or 'cs 976'.ti,ab,kf. or	39354

	'cs976'.ti,ab,kf. or 'biapenem'.ti,ab,kf. or 'cl 186815'.ti,ab,kf. or 'cl186815'.ti,ab,kf. or 'cli 86815'.ti,ab,kf. or 'cli86815'.ti,ab,kf. or 'l 627'.ti,ab,kf. or 'l627'.ti,ab,kf. or 'ljc 10627'.ti,ab,kf. or 'ljc10627'.ti,ab,kf. or 'rpx 2003'.ti,ab,kf. or 'rpx2003'.ti,ab,kf. or 'a 0026'.ti,ab,kf. or 'a0026'.ti,ab,kf. or 'alp 201'.ti,ab,kf. or 'alp201'.ti,ab,kf. or 'bla 857'.ti,ab,kf. or 'bla857'.ti,ab,kf. or 'farom'.ti,ab,kf. or 'faropenem'.ti,ab,kf. or 'fropenem'.ti,ab,kf. or 'furopenem'.ti,ab,kf. or 'ru 67655'.ti,ab,kf. or 'ru67655'.ti,ab,kf. or 'sun 5555'.ti,ab,kf. or 'sun5555'.ti,ab,kf. or 'sy 5555'.ti,ab,kf. or 'sy5555'.ti,ab,kf. or 'wy 49605'.ti,ab,kf. or 'wy49605'.ti,ab,kf. or 'ym 044'.ti,ab,kf. or 'ym044'.ti,ab,kf. or 'l 036'.ti,ab,kf. or 'l036'.ti,ab,kf. or 'ljc 11036'.ti,ab,kf. or 'ljc11036'.ti,ab,kf. or 'tebipenem'.ti,ab,kf. or 'l 084'.ti,ab,kf. or 'l084'.ti,ab,kf. or 'ljc 11084'.ti,ab,kf. or 'ljc11084'.ti,ab,kf. or 'me 1211'.ti,ab,kf. or 'me1211'.ti,ab,kf. or 'orapenem'.ti,ab,kf. or 'spr 994'.ti,ab,kf. or 'spr994'.ti,ab,kf. or (tebipenem adj3 pivoxil).ti,ab,kf. or 'ptz 601'.ti,ab,kf. or 'ptz601'.ti,ab,kf. or 'pz 601'.ti,ab,kf. or 'pz601'.ti,ab,kf. or 'razupenem'.ti,ab,kf. or 'sm 216601'.ti,ab,kf. or 'sm216601'.ti,ab,kf. or 'smp 601'.ti,ab,kf. or 'smp601'.ti,ab,kf. or 'bo 2727'.ti,ab,kf. or 'bo2727'.ti,ab,kf. or 'l 739428'.ti,ab,kf. or 'l739428'.ti,ab,kf. or 'lenapenem'.ti,ab,kf. or 'cp 65207'.ti,ab,kf. or 'cp 70429'.ti,ab,kf. or 'cp65207'.ti,ab,kf. or 'cp70429'.ti,ab,kf. or 'sulopenem'.ti,ab,kf. or 'cs 023'.ti,ab,kf. or 'cs023'.ti,ab,kf. or 'r 115685'.ti,ab,kf. or 'r 1558'.ti,ab,kf. or 'r115685'.ti,ab,kf. or 'r1558'.ti,ab,kf. or 'ro 4908463'.ti,ab,kf. or 'ro4908463'.ti,ab,kf. or 'tomopenem'.ti,ab,kf. or 'thienamycin'.ti,ab,kf. or 'tienamycin'.ti,ab,kf. or 'thienpenem'.ti,ab,kf.	
3	1 and 2	192
4	limit 3 to yr="2005 -Current"	126
5	4 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	113
6	Guideline/ or Practice Guideline/ or guideline*.ti,kf. or cpg.ti,kf. or consensus*.ti,kf. or guideline*.ab. /freq=2	265595
7	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	851725

8	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2929236
9	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or exp cohort studies/ or epidemiologic studies/ or ((multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/	8133476
10	5 and 6 - Guidelines	2
11	(5 and 7) not 10 - SR	12
12	(5 and 8) not (10 or 11) - RCT	15
13	(5 and 9) not (10 or 11 or 12) - Observationeel	31
14	10 or 11 or 12 or 13 - Totaal	60

5

Module 7. Optimale timing initiële drainage bij geïnfecteerde necrotiserende pancreatitis

Introduction (English)

Infected necrotizing pancreatitis is a potentially life-threatening condition. Current standard practice is to initiate broad-spectrum antibiotic therapy in patients with suspected or confirmed infected pancreatic necrosis and schedule endoscopic or percutaneous drainage. The question is what the optimal timing of initial drainage should be.

Search and select

A systematic review of the literature was performed to answer the following question(s):
What are the effects of immediate stent drainage in patients with clinical suspicion for, or documented, infected necrotizing pancreatitis, compared to antibiotic treatment first (and catheter drainage if no improvement)?

Table 1. PICO

Patients	Patients with clinical suspicion for, or documented, infected necrotizing pancreatitis
Intervention	Immediate catheter/stent drainage *
Control	Antibiotic treatment first, catheter drainage if no improvement
Outcomes	Mortality, new onset organ failure, quality of life, comprehensive complication index, length of hospital stay, number of invasive interventions
Other selection criteria	Study design: systematic reviews and randomized controlled trials

* The key aspect is early intervention without a period of watchful waiting.

Relevant outcome measures

The guideline panel considered mortality and new-onset organ failure as **critical** outcome measures for decision making; and quality of life, comprehensive complication index, length of hospital stay, and number of invasive interventions as **important** outcome measures for decision making.

The guideline panel defined the outcome measures as follows:

- Mortality, defined as mortality during index admission
- Number of invasive interventions, defined as endoscopic, percutaneous or surgical interventions

A priori, the guideline panel did not define the other outcome measures listed above but used the definitions used in the studies.

The guideline panel defined the following thresholds for minimal clinically important differences:

- Mortality: a relative risk of ≤ 0.90 or ≥ 1.10;
- Other dichotomous outcome measures: a relative risk of ≤ 0.80 or ≥ 1.25;
- Continuous outcome measures: 0.5 x median baseline standard deviation (SD) or 0.5 x standardized mean difference (SMD).

Search and select (Methods)

Systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2005 to the 21th of July 2025 for systematic reviews and RCTs. Systematic searches were completed using a combination of controlled

vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from two primary search concepts: (1) necrotizing pancreatitis; (2) stent drainage. Duplicates were removed using EndNote software. After deduplication a total of 650 records were imported for title/abstract screening. Although the PICO did not specify a strict time threshold for the intervention, the concept of early or immediate drainage was explicitly incorporated in the search strategy and study selection. Studies were included if the intervention was described as early or immediate, without watchful waiting or a step-up approach.

Initially, 12 studies were selected based on title and abstract screening. After reading the full text, 10 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and 2 studies were included.

Summary of literature

Description of studies

A total of two studies were included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias tables (under the tab 'Evidence tabellen').

Boxhoorn (2021) performed the POINTER (Postponed or Immediate Drainage of Infected Necrotizing Pancreatitis) trial, an multicentered RCT conducted at 22 centers collaborating within the Dutch Pancreatitis Study Group. The RCT involved patients with infected necrotizing pancreatitis, in which immediate catheter drainage within 24 hours after randomization once infected necrosis was compared with drainage that was postponed until the stage of walled-off necrosis was reached. Both treatments included treatment with antibiotics. A total of 104 patients were randomly assigned to immediate drainage (55 patients) or postponed drainage (49 patients). The trial was funded by Fonds NutsOhra and Amsterdam UMC. The funders had no role in the design or conduct of the trial or in the interpretation of the results. Access to the data was not restricted by confidentiality agreements.

Van Veldhuisen (2024) uses results from the same POINTER trial to compare the long-term outcomes of immediate drainage versus the postponed-drainage approach in patients with infected necrotizing pancreatitis.

Table 2. Characteristics and methodological quality assessment of included studies

Study	Participants	Comparison Intervention (I) and Comparison (C)	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Individual studies						
Boxhoorn, 2021	N at baseline I: 55 C: 49 Age (mean, SD) I: 60 ± 14 C: 59 ± 11 Male sex (n (%)) I: 32 (58) C: 32 (65)	I: Immediate catheter drainage included treatment with antibiotics and catheter drainage within 24 hours after randomization (which occurred as soon as infected necrosis was diagnosed on the basis of the aforementioned criteria). C: Postponed catheter drainage included treatment with antibiotics and supportive treatment aimed at postponing the drainage procedure until the stage of walled-off necrosis, when necrotic collections were largely or fully encapsulated.	6 months	Comprehensive Complication Index, mortality, new-onset organ failure [pulmonary, cardiovascular, renal, and multiple], length of hospital stay, number of invasive interventions (surgical, endoscopic, and radiologic interventions (catheter drainage and necrosectomy)	The trial was publicly funded and free from industry sponsorship. No relevant conflicts of interest were reported. Independent trial monitoring and a data and safety monitoring committee were in place. The study was conducted in high-volume expert centers, which strengthens internal validity but may limit generalisability to less specialized settings.	Low

Van Veldhuisen, 2024	N at baseline I: 55 C: 49 Age (mean, SD) I: 60 ± 14 C: 59 ± 11 Male sex (n (%)) I: 32 (58) C: 32 (65) *Out of 104 patients (Boxhoorn, 2011), 88 were re-evaluated with a median follow-up of 51 months*.	I: Immediate catheter drainage included treatment with antibiotics and catheter drainage within 24 hours after randomization (which occurred as soon as infected necrosis was diagnosed on the basis of the aforementioned criteria). C: Postponed catheter drainage included treatment with antibiotics and supportive treatment aimed at postponing the drainage procedure until the stage of walled-off necrosis, when necrotic collections were largely or fully encapsulated.	Median follow-up of 51 months	For the outcomes mortality, new-onset organ failure, length of hospital stay, and number of invasive interventions this study reported the new events after the initial 6-month follow-up. For the outcomes	The trial was publicly funded and free from industry sponsorship. No relevant conflicts of interest were reported. Independent trial monitoring and a data and safety monitoring committee were in place. The study was conducted in high-volume expert centers, which strengthens internal validity but may limit generalisability to less specialized settings.	Moderate
*For further details, see risk of bias table in the appendix						

Results

Mortality

Boxhoorn (2021) reported on the outcome mortality, defined as death within 6 months (POINTER trial). Mortality was 13% in the intervention group (7 of the 55 patients in the immediate-drainage group died within 6 months) as compared with 10% in the control group (5 of the 49 patients in the postponed-drainage group died within 6 months). The RR was of 1.25 (95% CI: 0.42 to 3.68), in favor of the control group. This difference is clinically relevant but highly imprecise given the wide confidence interval.

Van Veldhuisen (2024) reported on the outcome mortality during long-term follow-up of the POINTER trial, with a median follow-up of 51 months. The amount of new events after the initial 6-month follow-up (excluding events as initially reported in the POINTER trial) was 9% in the intervention group (4 of the 47 patients in the immediate-drainage group died) as compared with 10% in the control group (4 of the 41 patients in the postponed-drainage group died). The RR was 0.87 (95% CI: 0.23 to 3.27), in favor of the intervention group. This difference is clinically relevant but highly imprecise given the wide confidence interval.

New-onset organ failure

Boxhoorn (2021) reported on the outcome new-onset organ failure, defined as pulmonary, cardiovascular, or renal organ failure that was not present at the time of randomization. New-onset organ failure was 25% in the intervention group (14 of the 55 patients in the immediate-drainage group experienced new-onset organ failure within 6 months) as compared with 22% in the control group (11 of the 49 patients in the postponed-drainage group experienced new-onset organ failure within 6 months). The RR was of 1.13 (95% CI: 0.57 to 2.26), in favor of the control group. This difference is not clinically relevant but imprecise given the wide confidence interval.

Van Veldhuisen (2024) reported on the outcome new-onset organ failure during long-term follow-up, defined as pulmonary, cardiovascular, or renal organ failure that was not present at the time of randomization. The amount of new events after the initial 6-month follow-up (excluding events as initially reported in the POINTER trial) was 9% of patients in the intervention group (4 of 47 patients) compared with 5% in the control group (2 of 41 patients). The RR was 1.74 (95% CI: 0.34 to 9.04), in favor of the control group. This difference is clinically relevant but highly imprecise given the wide confidence interval.

Comprehensive Complication Index

Boxhoorn (2021) reported on the outcome Comprehensive Complication Index (CCI) score, calculated as the sum of all complications weighted according to severity. Continuous overall scores range from 0 (no complications) to 100 (death). The mean CCI score in the intervention group was 57 (95% CI: 50 to 75), as compared with a mean CCI score of 58 (95% CI: 50 to 67) in control group. The mean difference was -1 (95% CI: -12 to 10). This difference is not clinically relevant.

Length of hospital stay

Boxhoorn (2021) reported on the outcome length of stay in hospital, reported in days. The mean days of hospital stay in the intervention group was 59 (95% CI: 50 to 70), as compared with a mean days of hospital stay of 51 (95% CI: 40 to 65) in control group. The mean difference was 8 (95% CI: -9 to 23), in favor of the control group. This difference is not clinically relevant.

Van Veldhuisen (2024) reported on the outcome length of hospital stay related to pancreatitis after the initial 6-month follow-up (excluding events as initially reported in the POINTER trial). The median length of hospital stay in the intervention group was 0 days (IQR: 0 to 16), compared with 2 days (IQR: 0 to 5) in the control group.

Number of invasive interventions

Boxhoorn (2021) reported on the number of invasive interventions, defined as total surgical, endoscopic, and radiologic interventions for infected necrotizing pancreatitis. The mean total interventions in the intervention group was 4.4 (95% CI: 3.6 to 5.3), as compared with a mean total interventions of 2.6 (95% CI: 1.8 to 3.6) in control group. The mean difference was 1.8 (95% CI: 0.6 to 3.0), in favor of the control group. This difference is clinically relevant but imprecise given the wide confidence interval.

Van Veldhuisen (2024) reported on the number of invasive interventions, defined as the total number of surgical, endoscopic, and radiologic interventions for infected necrotizing pancreatitis after the initial 6-month follow-up (excluding events as initially reported in the POINTER trial). No events occurred during this time period.

Quality of life

Van Veldhuisen (2024) reported on quality of life at the end of long-term follow-up using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). Quality of life was assessed using the Physical Component Score (PCS) and Mental Component Score (MCS), with scores ranging from 0 to 100, where higher scores indicate better quality of life.
The mean PCS was 49 (SD 14) in the intervention group and 43 (SD 22) in the control group, resulting in a mean difference of 6 (95%CI: -2.3 to 14.3) points in favor of the intervention group. The mean MCS was 43 (SD 8) in the intervention group and 42 (SD 9) in the control group, resulting in a mean difference of 1 (95% CI: -2.8 to 4.8) point. Both differences are not clinically relevant but highly imprecise given the wide confidence interval.

Summary of Findings

PICO

Population: Patients with clinical suspicion for, or documented, infected necrotizing pancreatitis
Intervention: Immediate catheter/stent drainage <24 hours
Comparator: Antibiotic treatment first, catheter drainage if no improvement

Outcome vTimeframe	**Study results and measurements**	**Absolute effect estimates** Postponed catheter drainage (control)	 Immediate catheter drainage (intervention)	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality	Relative risk: 1.25 (CI 95% 0.42 - 3.68) Based on data from 104 participants in 1 studies	**102** per 1000	**128** per 1000 Difference: **26 more per 1000** (CI 95% 59 fewer - 273 more)	**Very low** Due to very serious imprecision[1]	We are uncertain whether immediate catheter drainage increases or decreases mortality at 6 months of follow-up
Mortality (long term)	Relative risk: 0.87 (CI 95% 0.23 - 3.27) Based on data from 88 participants in 1 studies	**98** per 1000	**85** per 1000 Difference: **13 fewer per 1000** (CI 95% 75 fewer - 222 more)	**Very low** Due to very serious imprecision, due to serious risk of bias, and due to serious indirectness[2]	We are uncertain whether immediate catheter drainage increases or decreases mortality (long term)
New-onset organ failure	Relative risk: 1.13 (CI 95% 0.57 - 2.26) Based on data from 104 participants in 1 studies	**224** per 1000	**253** per 1000 Difference: **29 more per 1000** (CI 95% 96 fewer - 282 more)	**Low** Due to very serious imprecision[3]	Immediate catheter drainage may have little or no difference on new-onset organ failure at 6 months of follow-up
New-onset organ failure (long term)	Relative risk: 1.74 (CI 95% 0.34 - 9.04) Based on data from 88 participants in 1 studies	**49** per 1000	**85** per 1000 Difference: **36 more per 1000** (CI 95% 32 fewer - 394 more)	**Very low** Due to very serious imprecision, due to serious risk of bias, and due to serious indirectness[4]	We are uncertain whether immediate catheter drainage increases or decreases new-onset organ failure (long term)

Comprehensive Complication Index	Measured by: Comprehensive Complication Index score Scale: 0 - 100 Lower better Based on data from 104 participants in 1 studies	**58** Mean **57** Mean Difference: **MD 1 lower** (CI 95% 12 lower - 10 higher)	**Moderate** Due to serious imprecision[5]	Immediate catheter drainage may have little or no difference on new-onset organ failure (long term)
Length of hospital stay	Measured by: mean days of hospital stay Scale: - Lower better Based on data from 104 participants in 1 studies	**51** daysMean **59** daysMean Difference: **MD 8 higher** (CI 95% 9 lower - 23 higher)	**Moderate** Due to serious imprecision[6]	Immediate catheter drainage probably has little or no difference on length of hospital stay at 6 months of follow-up
Length of hopsital stay (long term)	Measured by: mean days of hospital stay Scale: - Lower better Based on data from 88 participants in 1 studies	**2** daysMedian **0** daysMedian	**No GRADE** (data was too limited to perform GRADE-analysis)[6]	Data was too limited regarding the effect of immediate catheter drainage on length of hospital stay (long term)
Number of invasive interventions	Measured by: Total surgical, endoscopic, and radiologic interventions for infected necrosis Scale: - Lower better Based on data from 104 participants in 1 studies	**2.6** Mean **4.4** Mean Difference: **MD 1.8 higher** (CI 95% 0.6 lower - 3.0 lower)	**Low** Due to very serious imprecision[8]	Immediate catheter drainage may increase number of invasive interventions at 6 months of follow-up slightly
Number of invasive interventions (long term)	Measured by: Total surgical, endoscopic, and radiologic interventions for infected necrosis Scale: - Lower better Based on data from 88 participants in 1 studies	**0** Median **0** Median	**No GRADE** (data was too limited to perform GRADE-analysis)[9]	Data was too limited regarding the effect of immediate catheter drainage on the number of invasive interventions (long term)

Quality of life - PCS (long term)	Measured by: Physical Component Score from SF-36 Scale: 0 - 100 High better Based on data from 100 participants in 1 studies	**43** Mean **49** Mean Difference: **MD 6 higher** (CI 95% 2.3 lower - 14.3 higher)	**Very low** Due to serious imprecision, serious risk of bias and serious indirectness[10]	We are uncertain whether immediate catheter drainage increases or decreases quality of life - PCS (long term)
Quality of life - MCS (long term)	Measured by: Mental Component Score from SF-36 Scale: 0 - 100 High better Based on data from 100 participants in 1 studies	**42** Mean **43** Mean Difference: **MD 1 higher** (CI 95% 2.8 lower - 4.8 higher)	**Very low** Due to serious imprecision, risk of bias, and serious indirectness[11]	We are uncertain whether immediate catheter drainage increases or decreases quality of life - MCS (long term)

17. ***Imprecision: very serious.*** *Wide confidence intervals;*
18. ***Imprecision: very serious.*** *Wide confidence intervals;* ***Risk of bias: serious.*** *Loss to follow-up;* ***Indirectness: serious.*** *Outcomes measured after 6 months; uncertainty whether effect is attributable to the intervention or to the natural course of the disease***.**
19. ***Imprecision: very serious.*** *Wide confidence intervals;*
20. ***Imprecision: very serious.*** *Wide confidence intervals;* ***Risk of bias: serious.*** *Loss to follow-up;* ***Indirectness: serious.*** *Outcomes measured after 6 months; uncertainty whether effect is attributable to the intervention or to the natural course of the disease***.**
21. ***Imprecision: serious.*** *Low sample size. As the confidence interval is small, we test the optimal information size using the following calculator: Power/Sample Size Calculator. The optimal information size should be 13477 per arm, thus 26954 total, which is more than the 104 patients in the study from Boxhoorn (2021);*
22. ***No GRADE.*** *due to effect estimate based on medians and approximated SDs;*
23. ***Imprecision: very serious.*** *Wide confidence intervals, Low number of events;*
24. ***No GRADE.*** *Low number of events and due to effect estimate based on medians and approximated SDs;*
25. ***Imprecision: serious.*** *Wide confidence intervals;*
26. ***Imprecision: serious.*** *Wide confidence intervals;* ***Risk of bias: serious.*** *Loss to follow-up;* ***Indirectness: serious.*** *Outcomes measured after 6 months; uncertainty whether effect is attributable to the intervention or to the natural course of the disease***.**
27. ***Imprecision:*** *serious. Wide confidence intervals;* ***Risk of bias: serious.*** *Loss to follow-up;* ***Indirectness: serious.*** *Outcomes measured after 6 months; uncertainty whether effect is attributable to the intervention or to the natural course of the disease***.**

Kennisvragen

Tijdens de ontwikkeling van deze module is gebleken dat er binnen deze module nog te weinig bewijs is voor de onderbouwing van de aanbeveling en dus kennisvragen bestaan. De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk.

Kennisvraag:
Leidt gericht antibioticabeleid tot een betere uitkomst en minder noodzaak tot interventies?

P: Patiënten met geïnfecteerde pancreasnecrose.
I: Behandeling infecties via een best-practice protocol gebasseerd op antibiotic stewardship principes
C: Standaardzorg.
O: Mortaliteit, orgaanfalen, optreden van resistentievorming, duur ziekenhuisopname, noodzaak tot interventie.

Implementeren-tabel

Vraag	***Antwoord:*** *Kruis aan en licht toe/ beschrijf*		***Toelichting keuze:***
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**x**	**Ongewenste praktijkvariatie**	Grote praktijkvariatie in Nederland
	x	**Nieuwe evidentie**	POINTER trial
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**x**	**< 1000**	
		< 5000	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?	**x**	**Ja**	Verwant aan module - antibioticumbeleid
		Nee	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)			

Zorgverleners (artsen en verpleegkundigen)			
Patiënt/ cliënt (naasten)			
Sociale context			
Organisatorische context		Geïnfecteerde necrotiserende pancreatitis is relatief zeldzaam, kleinere ziekenhuizen zien dit misschien een paar keer per jaar	Endoscopische, interventieradiologische en chirurgische expertise is in Nederland ruim aanwezig < 1 uur reistijd.
Financiële en juridische context			
I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
		Patiënt/ cliënt (naaste)	
	x	Professional	
	x	Beroepsvereniging, nl	
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**x**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*	**x**	Ja	Publicatie in Nederlandse vakbladen; NVMDL, NVvH, V&VN, NAPA, NVIR, NVIC, NVMM
		Nee	
	x	Ja *	

I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*		Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Literatuur

Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL, Bouwense SAW, Bruno MJ, Cappendijk VC, Dejong CHC, van Duijvendijk P, van Eijck CHJ, Fockens P, Francken MFG, van Goor H, Hadithi M, Hallensleben NDL, Haveman JW, Jacobs MAJM, Jansen JM, Kop MPM, van Lienden KP, Manusama ER, Mieog JSD, Molenaar IQ, Nieuwenhuijs VB, Poen AC, Poley JW, van de Poll M, Quispel R, Römkens TEH, Schwartz MP, Seerden TC, Stommel MWJ, Straathof JWA, Timmerhuis HC, Venneman NG, Voermans RP, van de Vrie W, Witteman BJ, Dijkgraaf MGW, van Santvoort HC, Besselink MG; Dutch Pancreatitis Study Group. Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis. N Engl J Med. 2021 Oct 7;385(15):1372-1381. doi: 10.1056/NEJMoa2100826. PMID: 34614330.

Boxhoorn L, Verdonk RC, Besselink MG, Boermeester M, Bollen TL, Bouwense SA, Cappendijk VC, Curvers WL, Dejong CH, van Dijk SM, van Dullemen HM, van Eijck CH, van Geenen EJ, Hadithi M, Hazen WL, Honkoop P, van Hooft JE, Jacobs MA, Kievits JE, Kop MP, Kouw E, Kuiken SD, Ledeboer M, Nieuwenhuijs VB, Perk LE, Poley JW, Quispel R, de Ridder RJ, van Santvoort HC, Sperna Weiland CJ, Stommel MW, Timmerhuis HC, Witteman BJ, Umans DS, Venneman NG, Vleggaar FP, van Wanrooij RL, Bruno MJ, Fockens P, Voermans RP; Dutch Pancreatitis Study Group. Comparison of lumen-apposing metal stents versus double-pigtail plastic stents for infected necrotising pancreatitis. Gut. 2023 Jan;72(1):66-72. doi: 10.1136/gutjnl-2021-325632. Epub 2022 Jun 14. PMID: 35701094.

Francken MFG, Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL, Bouwense SAW, Bruno MJ, Cappendijk VC, van Duijvendijk P, van Eijck CHJ, Fockens P, van Goor H, Hadithi M, Hallensleben NDL, Haveman JW, Jacobs MAJM, Jansen JM, Kop MPM, van Lienden KP, Manusama ER, Mieog JSD, Molenaar IQ, Nieuwenhuijs VB, Poen AC, Poley JW, van de Poll M, Quispel R, Römkens TEH, Schwartz MP, Seerden TC, Stommel MWJ, Straathof JWA, Timmerhuis HC, Venneman NG, Voermans RP, van de Vrie W, van Santvoort HC, Besselink MG, Dijkgraaf MGW. Cost-effectiveness of immediate versus postponed intervention for infected necrotizing pancreatitis: planned secondary analysis of the POINTER trial. Br J Surg. 2025 Mar 28;112(4):znaf071. doi: 10.1093/bjs/znaf071. PMID: 40276899; PMCID: PMC12022604.

Ke L, Li G, Mao W, Doig G, Chen T, Li C, Qu C, Wang L, Gao L, He W, Xia L, Guo F, Lin Y, Feng Q, Liu Z, Li B, Jaber S, Papachristou G, Zhu Y, Liu Y, Windsor J, Tong Z, Li W; Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG). Early versus delayed catheter drainage for patients with necrotizing pancreatitis and early persistent organ failure (TIMING): a multicenter randomized controlled trial. Intensive Care Med. 2025 Aug;51(8):1431-1441. doi: 10.1007/s00134-025-08020-x. Epub 2025 Jul 14. PMID: 40658249.

Vaccari M, Tudor T, Perteghella A. Costs associated with the management of waste from healthcare facilities: An analysis at national and site level. Waste Manag Res. 2018 Jan;36(1):39-47. doi: 10.1177/0734242X17739968. Epub 2017 Nov 14. PMID: 29132259.

van Grinsven J, van Brunschot S, van Santvoort HC; Dutch Pancreatitis Study Group. The Value of a 24/7 Online Nationwide Multidisciplinary Expert Panel for Acute

Necrotizing Pancreatitis. Gastroenterology. 2017 Mar;152(4):685-688.e6. doi: 10.1053/j.gastro.2017.01.040. Epub 2017 Feb 3. PMID: 28163063.

Van Veldhuisen CL, Sissingh NJ, Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bouwense SAW, Bruno MJ, Cappendijk VC, van Duijvendijk P, van Eijck CHJ, Fockens P, van Goor H, Hadithi M, Haveman JW, Jacobs MAJM, Jansen JM, Kop MPM, Manusama ER, Mieog JSD, Molenaar IQ, Nieuwenhuijs VB, Poen AC, Poley JW, Quispel R, Römkens TEH, Schwartz MP, Seerden TC, Dijkgraaf MGW, Stommel MWJ, Straathof JWA, Venneman NG, Voermans RP, van Hooft JE, van Santvoort HC, Besselink MG; Dutch Pancreatitis Study Group. Long-Term Outcome of Immediate Versus Postponed Intervention in Patients With Infected Necrotizing Pancreatitis (POINTER): Multicenter Randomized Trial. Ann Surg. 2024 Apr 1;279(4):671-678. doi: 10.1097/SLA.0000000000006001. Epub 2023 Jul 17. PMID: 37450701; PMCID: PMC10922655.

Bijlagen bij module Optimale timing initiële drainage

Risk of Bias tables

5 **Research question: What are the effects of immediate stent drainage in patients with clinical suspicion for, or documented, infected necrotizing pancreatitis, compared to antibiotic treatment first (and catheter drainage if no improvement)?**

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Boxhoorn, 2021	Definitely yes; Reason: Centralized computer-generated randomization with variable block sizes and stratification (organ	Definitely yes; Reason: Allocation performed via a centrally operated computer system,	Probably yes; Reason: Patients: Definitely no; Healthcare providers: Definitely no; Outcome assessors:	Definitely yes; Reason: No missing data for the primary outcome and very limited missing data for secondary outcomes;	Definitely yes; Reason: Trial was prospectively registered and all prespecified primary and secondary	Probably yes; Reason: Reason: No other important sources of bias identified; independent	**LOW**

	failure, disease duration, hospital volume).	ensuring concealment prior to assignment.	Definitely yes (independent adjudication committee blinded to treatment allocation); Data collectors/analysts: Probably yes.	intention-to-treat analysis used.	outcomes were reported.	monitoring and funders had no role in study conduct or analysis.	
Van Veldhuisen, 2024	Definitely yes; Reason: Centralized computer-generated randomization with variable block sizes and stratification (organ failure, disease duration, hospital volume).	Definitely yes; Reason: Allocation performed via a centrally operated computer system, ensuring concealment prior to assignment.	Probably yes; Reason: Patients: Definitely no; Healthcare providers: Definitely no; Outcome assessors: Definitely yes (independent adjudication committee blinded to treatment allocation); Data collectors/analysts: Probably yes.	Definitely no; Reason: Out of 104 patients, 88 were re-evaluated with a median followup of 51 months.	Definitely yes; Reason: Trial was prospectively registered and all prespecified primary and secondary outcomes were reported.	Probably yes; Reason: Reason: No other important sources of bias identified; independent monitoring and funders had no role in study conduct or analysis.	**Some concerns (all outcomes)**

Table of excluded studies

Reference	Reason for exclusion
Francken MFG, Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL, Bouwense SAW, Bruno MJ, Cappendijk VC, van Duijvendijk P, van Eijck CHJ, Fockens P, van Goor H, Hadithi M, Hallensleben NDL, Haveman JW, Jacobs MAJM, Jansen JM, Kop MPM, van Lienden KP, Manusama ER, Mieog JSD, Molenaar IQ, Nieuwenhuijs VB, Poen AC, Poley JW, van de Poll M, Quispel R, Römkens TEH, Schwartz MP, Seerden TC, Stommel MWJ, Straathof JWA, Timmerhuis HC, Venneman NG, Voermans RP, van de Vrie W, van Santvoort HC, Besselink MG, Dijkgraaf MGW. Cost-effectiveness of immediate versus postponed intervention for infected necrotizing pancreatitis: planned secondary analysis of the POINTER trial. Br J Surg. 2025 Mar 28;112(4):znaf071. doi: 10.1093/bjs/znaf071. PMID: 40276899; PMCID: PMC12022604.	Wrong outcome, cost effectiveness.
Shenvi S, Gupta R, Kang M, Khullar M, Rana SS, Singh R, Bhasin DK. Timing of surgical intervention in patients of infected necrotizing pancreatitis not responding to percutaneous catheter drainage. Pancreatology. 2016 Sep-Oct;16(5):778-87. doi: 10.1016/j.pan.2016.08.006. Epub 2016 Aug 13. PMID: 27592206.	Wrong study population (patients with IPN and not responding on drainage),
Ke L, Dong X, Chen T, Doig GS, Li G, Ye B, Zhou J, Xiao X, Tong Z, Li W; Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG). Early on-demand drainage or standard management for acute pancreatitis patients with acute necrotic collections and persistent organ failure: A pilot randomized controlled trial. J Hepatobiliary Pancreat Sci. 2021 Apr;28(4):387-396. doi: 10.1002/jhbp.915. Epub 2021 Mar 18. PMID: 33595879.	Wrong study population (patients with IPN and not responding on drainage),
Ke L, Li G, Mao W, Doig G, Chen T, Li C, Qu C, Wang L, Gao L, He W, Xia L, Guo F, Lin Y, Feng Q, Liu Z, Li B, Jaber S, Papachristou G, Zhu Y, Liu Y, Windsor J, Tong Z, Li W; Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG). Early versus delayed catheter drainage for patients with necrotizing pancreatitis and early persistent organ failure (TIMING): a multicenter randomized controlled trial. Intensive Care Med. 2025 Aug;51(8):1431-1441. doi: 10.1007/s00134-025-08020-x. Epub 2025 Jul 14. PMID: 40658249.	Wrong study population (patients with IPN and not responding on drainage),
Hu Y, Zeng Q, Ren S, Wang K. Immediate versus postponed drainage for infected necrotizing pancreatitis: A systematic review and meta-analysis. Asian J Surg. 2023 Apr;46(4):1602-1603. doi: 10.1016/j.asjsur.2022.09.079. Epub 2022 Oct 12. PMID: 36241519.	Wrong study population (patients with IPN and not responding on drainage),
Ricci C, Pagano N, Ingaldi C, Frazzoni L, Migliori M, Alberici L, Minni F, Casadei R. Treatment for Infected Pancreatic Necrosis Should be Delayed, Possibly Avoiding an Open Surgical Approach: A Systematic Review and Network Meta-analysis. Ann Surg. 2021 Feb 1;273(2):251-257. doi: 10.1097/SLA.0000000000003767. PMID: 31972645.	Wrong study population (patients with IPN and not responding on drainage),
Zhu L, Shen J, Fu R, Lu X, Du L, Jiang R, Zhang M, Shi Y, Jiang K, Shi Y. Early versus Delayed Minimally Invasive Intervention for Acute Necrotizing Pancreatitis: An Updated Systematic Review and Meta-Analysis. Dig Surg. 2022;39(5-6):224-231. doi: 10.1159/000529465. Epub 2023 Feb 7. PMID: 36750033.	Wrong study population (patients with IPN and not responding on drainage),
Nakai Y, Shiomi H, Hamada T, Ota S, Takenaka M, Iwashita T, Sato T, Saito T, Masuda A, Matsubara S, Iwata K, Mukai T, Isayama H, Yasuda I; WONDERFUL study group in Japan. Early versus delayed interventions for necrotizing pancreatitis: A systematic review and meta-analysis. DEN Open. 2022 Oct 10;3(1):e171. doi: 10.1002/deo2.171. PMID: 36247314; PMCID: PMC9549879.	Wrong study population (patients with IPN and not responding on drainage),
Mouli VP, Sreenivas V, Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. Gastroenterology. 2013 Feb;144(2):333-340.e2. doi:	Wrong study population (patients with IPN and not responding on drainage),

10.1053/j.gastro.2012.10.004. Epub 2012 Oct 12. PMID: 23063972.	
Gao L, Zhang H, Li G, Ye B, Zhou J, Tong Z, Ke L, Windsor JA, Li W; Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG). The clinical outcome from early versus delayed minimally invasive intervention for infected pancreatic necrosis: a systematic review and meta-analysis. J Gastroenterol. 2022 Jun;57(6):397-406. doi: 10.1007/s00535-022-01876-6. Epub 2022 Apr 29. PMID: 35488104.	Wrong study population (patients with IPN and not responding on drainage),

Literature search strategy

Zoekstrategie Embase.com 21 juli 2025

No.	*Query*	*Results*
#1	'pancreas necrosis'/exp OR 'acute pancreatitis'/exp OR 'acute hemorrhagic pancreatitis'/exp OR (('pancreatitis'/exp OR pancreatit*:ti,ab,kw OR ((pancrea* NEAR/3 inflammation*):ti,ab,kw)) AND ('necrosis'/de OR acut*:ti,ab,kw OR necroti*:ti,ab,kw OR necros*:ti,ab,kw))	76152
#2	'stent'/exp OR 'drainage'/exp OR 'drainage/aspiration system'/exp OR 'drainage tube'/exp OR 'abscess drainage'/exp OR 'surgical drainage'/exp OR 'catheter'/exp OR 'catheter drainage'/exp OR (((immediate* OR earl* OR postpon* OR 'post pon*' OR late* OR delayed OR prolonged) NEAR/3 (interve* OR surg*)):ti,ab,kw) OR stent*:ti,ab,kw OR drain*:ti,ab,kw OR catheter*:ti,ab,kw	1280694
#3	#1 AND #2	13028
#4	#3 AND [2005-2025]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'clinical trial':dtype) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	5506
#5	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR	1137786

	medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	
#6	'randomized controlled trial'/exp OR (((pragmatic OR practical) NEAR/1 'clinical trial'):ti,ab) OR ((('non inferiority' OR noninferiority OR superiority OR equivalence) NEXT/3 trial):ti,ab) OR rct:ti OR randomly*:ti,ab OR randomi*:ti,ab OR 'random* control*':ti,ab	2191378
#7	#4 AND #5 - SR	299
#8	#4 AND #6 NOT #7 - RCT	307
#9	#7 OR #8 - Totaal	606

Zoekstrategie Ovid/Medline 21 juli 2025

#	Searches	Results
1	exp Pancreatitis, Acute Hemorrhagic/ or exp Pancreatitis, Acute Necrotizing/ or ((exp Pancreatitis/ or pancreatit*.ti,ab,kf. or (pancrea* adj3 inflammation*).ti,ab,kf.) and (exp Acute Disease/ or Necrosis/ or acut*.ti,ab,kf. or necroti*.ti,ab,kf. or necros*.ti,ab,kf.))	43472
2	exp Stents/ or exp Drainage/ or exp Catheters/ or ((immediate* or earl* or postpon* or post pon* or late* or delayed or prolonged) adj3 (interve* or surg*)).ti,ab,kf. or stent*.ti,ab,kf. or drain*.ti,ab,kf. or catheter*.ti,ab,kf.	729329
3	1 and 2	5084
4	limit 3 to yr="2005 -Current"	3339
5	4 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	3153
6	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or (((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	847263

7	exp randomized controlled trial/ or randomi*.ti,ab. or rct?.ti,ab. or randomly.ti,ab. or "random* control*".ti,ab. or ((pragmatic or practical) adj "clinical trial*").ti,ab. or ((non-inferiority or noninferiority or superiority or equivalence) adj3 trial*).ti,ab.	1450090
8	5 and 6 - SR	161
9	(5 and 7) not 8 - RCT	178
10	8 or 9 - Totaal	339

Module 8. Necrosectomie bij geïnfecteerde necrotiserende pancreatitis

Introduction (English)

Drainage of infected pancreatic necrosis is indicated when antibiotic therapy fails to achieve source control. When insufficient clinical improvement is achieved after drainage, a necrosectomy is indicated. This is typically performed transluminally via endoscopy or percutaneously via video-assisted retroperitoneal debridement (VARD). Necrosectomy may be a time-consuming procedure, and carries a risk of bleeding. At present, the indication and timing of necrosectomy are largely based on the physician's assessment and experience. Recently, studies have suggested that in selected patients it may be worthwhile to perform the endoscopic necrosectomy already at the time of the initial transgastric drainage (or very shortly thereafter). The rationale for this approach is mostly to reduce the number of endoscopic procedures required.

Search and select

A systematic review of the literature was performed to answer the following question(s): What is the optimal timing for necrosectomy in patients with infected pancreatic necrosis?

Table 1. PICO

Patients	Patients with infected necrotizing pancreatitis without clinical improvement following antibiotic treatment and in whom catheter drainage (either endoscopic or percutaneous) is planned
Intervention	Immediate necrosectomy after the collection has been entered with a drain
Control	Step-up approach which involves awaiting the impact of the first drainage for 48-72 hours, possible a repeated drainage, and only performing a necrosectomy in case of no clinical improvement after drainage
Outcomes	Mortality, number of invasive interventions (for necrosis), quality of life, length of hospital stay, comprehensive complication index, new onset organ failure
Other selection criteria	Study design: systematic reviews, randomized controlled trials, other non-comparative studies

Relevant outcome measures

The guideline panel considered mortality, organ failure and the comprehensive complication index as **critical** outcome measures for decision making; and hospital stay, number of procedures, quality of life and costs as **important** outcome measures for decision making.

The guideline panel defined the outcome measures as follows:

- Mortality, defined as mortality during index admission
- Number of invasive interventions, defined as endoscopic, percutaneous or surgical interventions

A priori, the guideline panel did not define the other outcome measures listed above but used the definitions used in the studies.

The guideline panel defined the following thresholds for minimal clinically important differences:

- Mortality: a relative risk of ≤ 0.91 or ≥ 1.10;
- Other dichotomous outcome measures: a relative risk of ≤ 0.80 or ≥ 1.25;
- Continuous outcome measures: 0.5 x median baseline standard deviation (SD) or 0.5 x standardized mean difference (SMD).

Search and select (Methods)

A systematic literature search was performed by a medical information specialist using the following bibliographic databases: Embase.com and Ovid/Medline. Both databases were searched from 2005 to the 14th of Juli 2025 for systematic reviews, RCTs and observational studies. Systematic searches were completed using a combination of controlled vocabulary/subject headings (e.g., Emtree-terms, MeSH) wherever they were available and natural language keywords. The overall search strategy was derived from two primary search concepts: (1) necrotizing pancreatitis; (2) necrosectomy. Duplicates were removed using EndNote software. After deduplication a total of 788 records were imported for title/abstract screening.

Initially, 13 studies were selected based on title and abstract screening. After reading the full text, 12 studies were excluded (see the exclusion table under the tab 'Evidence tabellen'), and one study was included

Summary of literature

Description of studies

One study was included in the analysis of the literature. Important study characteristics and results are summarized in table 2. The assessment of the risk of bias is summarized in the risk of bias table (under the tab 'Evidence tabellen').

Bang (2024) performed a single-blinded, randomised trial at six tertiary hospitals (5 in the USA and one in India). Seventy patients were included between Nov 27, 2019, and Oct 26, 2022 and received either upfront necrosectomy (n=37) or step-up treatment. "Included were adult patients (aged ≥18 years) admitted to the hospital with confirmed or suspected infected pancreatic or peripancreatic necrosis, or both, of any size and any number of loculations, with the extent of necrosis of at least 33%, warranting intervention, and being amenable to endoscopic ultrasound-guided drainage. Exclusion criteria were previous surgical, percutaneous, or endoscopic drainage or necrosectomy, pancreatitis due to trauma

or surgical intervention, pregnancy, irreversible coagulopathy (international normalised ratio >1.5; thrombocytopenia with platelet count <50 000 platelets per µL), and use of anticoagulants that cannot be discontinued for the procedure." "In the upfront necrosectomy group, necrotic debridement was performed immediately after stent placement in the same treatment session." "In the step-up group, direct endoscopic necrosectomy or additional drainage was performed at a subsequent treatment session if there was no clinical improvement after lumen-apposing metal stent placement." The primary outcome of the study was total number of reinterventions performed per patient to achieve treatment success during admission and until 6 months after the index intervention. This was defined as symptom relief in conjunction with disease resolution on CT. Reinterventions included any endoscopic or radiological procedures performed for necrosectomy or additional drainage after the index intervention, excluding the follow-up procedure at 4 weeks for stent removal. The secondary outcomes were treatment success; disease-related adverse events; procedure-related adverse events; clinical improvement (72h after index intervention); readmissions due to underlying disease or procedure-related symptoms or events; pancreatic exocrine and endocrine status; length of hospital stay; intensive care unit (ICU) stay; technical success for endoscopic ultrasound-guided drainage; technical success for endoscopic necrosectomy; and overall treatment costs.

Table 2. Characteristics of included studies

Study	Participants	Comparison	Follow-up	Outcome measures	Comments	Risk of bias (per outcome measure)*
Bang, 2024	N at baseline Intervention: 37 Control: 33 Age (mean, SD) Intervention: 45.7 ± 14.4 Control: 53.2 ± 14.9 Sex Intervention: 26 male Control: 20 male	Intervention: upfront necrosectomy Control: step-up approach	6 months after discharge	Mortality from index to 6 months' follow-up Number of reinterventions during admission and until 6 months' follow-up Post-procedure length of hospital stay Disease-related adverse events and procedure-related adverse events	Single-blinded	High (for mortality, number of reinterventions, length of hospital stay, adverse events)

*For further details, see risk of bias table in the appendix

Results

Mortality (crucial)
Bang (2024) reported on the outcome mortality. In the upfront necrosectomy group 0/37 (0%) patients died, compared to 2/33 (6%) patients in the step-up approach group. Risk ratio (RR, 95%CI) was 0.18 (0.01 to 3.60), in favor of the upfront necrosectomy group. This difference is clinically relevant but highly imprecise given the wide confidence interval.

Number of invasive interventions (for necrosis, defined as endoscopic, percutaneous or surgical interventions) (important)
Bang (2024) reported on the outcome total number of reinterventions per patient to achieve treatment success from index intervention to 6 months' follow-up. In the upfront necrosectomy group the median number of reinterventions was 1 (IQR: 0 to 1), compared to 2 (IQR: 1 to 4) in the step-up approach group.

Quality of life (important)
Bang (2024) did not report on the outcome quality of life.

Length of hospital stay (important)
Bang (2024) reported on the outcome length of hospital stay from index intervention to discharge. In the upfront necrosectomy group the median length of hospital stay was 9 days (IQR: 7 to 20), compared to 19 days (IQR: 9 to 33) in the step-up approach group.

Comprehensive complication index (crucial)
Bang (2024) did not report on the outcome comprehensive complication index, but did report on disease-related and procedure-related adverse events.
In the upfront necrosectomy group 12/37 (32%) patients showed disease-related adverse events, compared to 16/33 (48%) patients in the step-up approach group. Risk ratio (RR, 95%CI) was 0.67 (0.37 to 1.20), in favor of the upfront necrosectomy group. This difference is clinically relevant but highly imprecise given the wide confidence interval.
In the upfront necrosectomy group 4/37 (11%) patients showed procedure-related adverse events, compared to 8/33 (24%) patients in the step-up approach group. Risk ratio (RR, 95%CI) was 0.45 (0.15 to 1.35), in favor of the upfront necrosectomy group. This difference is clinically relevant but highly imprecise given the wide confidence interval.

New onset organ failure (crucial)
Bang (2024) did not report on the outcome new onset organ failure.

Summary of findings

Population: Patients with infected necrotizing pancreatitis without clinical improvement following antibiotic treatment and in whom catheter drainage (either endoscopic or percutaneous) is planned.
Intervention: Immediate necrosectomy after the collection has been entered with a drain.
Comparator: Step-up approach which involves awaiting the impact of the first drainage for 48-72 hours, possible a repeated drainage and only a necrosectomy hereafter.

Outcome	**Study results and measurements**	**Absolute effect estimates** Immediate necrosectomy	Step-up approach	**Certainty of the evidence** (Quality of evidence)	**Summary**
Mortality (critical)	Relative risk 0.18 (CI 95% 0.01 – 3.60) Based on data from 70 participants in 1 study Follow up 6 months	**11** per 1000	**60** per 1000 Difference: **49 fewer per 1000** (CI 95% 60 fewer - 157 more)	**Very low** Due to very serious imprecision[1]	The evidence is very uncertain about the effect of immediate necrosectomy on mortality when compared with step-up approach in patients with infected necrotizing pancreatitis. (Bang, 2024)
Number of invasive interventions (important)	Based on data from 70 participants in 1 study Follow up 6 months	**27** per 1000 median	**60** per 1000 median	**No GRADE** (data was too limited to perform GRADE-analysis)[2]	Data was too limited about the effect of immediate necrosectomy on number of invasive interventions when compared with step-up approach in patients with infected necrotizing pancreatitis. (Bang, 2024)
Quality of life (important)	-	-		**No GRADE** (no evidence was found)	No evidence was found regarding the effect of immediate necrosectomy on quality of life when compared with step-up approach in patients with infected necrotizing pancreatitis. (Bang, 2024)
Length of hospital stay (important)	Based on data from 70 participants in 1 study Follow up 6 months	**27** per 1000 median	**60** per 1000 median	**No GRADE** (data was too limited to perform GRADE-analysis)[3]	Data was too limited about the effect of immediate necrosectomy on length of hospital stay when compared with step-up approach in patients with infected

				necrotizing pancreatitis. (Bang, 2024)
Comprehensive complication index - disease-related adverse events (critical)	Relative risk 0.67 (CI 95% 0.37 – 1.20) Based on data from 70 participants in 1 study Follow up 6 months	**325** per 1000 **485** per 1000 Difference: **160 fewer per 1000** (CI 95% 305 fewer - 97 more)	**Very low** Due to very serious risk of bias, due to serious imprecision[4]	The evidence is very uncertain about the effect of immediate necrosectomy on disease-related adverse events when compared with step-up approach in patients with infected necrotizing pancreatitis. (Bang, 2024)
Comprehensive complication index - procedure-related adverse events (critical)	Relative risk 0.45 (CI 95% 0.15 – 1.35) Based on data from 70 participants in 1 study Follow up 6 months	**109** per 1000 **242** per 1000 Difference: **133 fewer per 1000** (CI 95% 206 fewer - 85 more)	**Very low** Due to very serious risk of bias, due to very serious imprecision[5]	The evidence is very uncertain about the effect of immediate necrosectomy on procedure-related adverse events when compared with step-up approach in patients with infected necrotizing pancreatitis. (Bang, 2024)
New onset organ failure (critical)	-	**-**	**No GRADE** (no evidence was found)	No evidence was found regarding the effect of immediate necrosectomy on new onset organ failure when compared with step-up approach in patients with infected necrotizing pancreatitis. (Bang, 2024)

28. **Imprecision: very serious**. Due to overlap of both limits of the 95% confidence interval with the minimal clinically important difference and low number of patients (<100) and data of only one study;
29. **No GRADE.** due to effect estimate based on medians and approximated SDs;
30. **No GRADE.** due to effect estimate based on medians and approximated SDs;
31. **Risk of Bias: very serious.** Due to lack of blinding of endoscopists.
    Imprecision: serious. Due to overlap of the upper limit of the 95% confidence interval with the minimal clinically important difference and low number of patients (<100) and data of only one study;
32. **Risk of Bias: very serious.** Due to lack of blinding of endoscopists.
    Imprecision: very serious. Due to overlap of both limits of the 95% confidence interval with the minimal clinically important difference and low number of patients (<100) and data of only one study;

Kennisvragen

De werkgroep meent dat (vervolg)onderzoek wenselijk is om in de toekomst een duidelijker antwoord te kunnen geven op vragen uit de praktijk. Een belangrijke kennishiaat op dit moment is wat de optimale necrosectomietechniek is.

Kennisvraag 1: Leidt een volledige necrosectomie in één sessie tot minder mortaliteit, orgaanfalen en aantal invasieve procedures?

P: Patiënten met geïnfecteerde pancreasnecrose met reeds endoscopische of percutane drainage, maar met uitblijven van klinische verbetering, waarvoor een necrosectomie geïndiceerd is.
I: Volledige necrosectomie tot alle necrose, bereikbaar voor endoscopist of chirurg, verwijderd is, ongeacht de duur van de procedure.
C: Partiële necrosectomie, maximaal 90 minuten.
O: Mortaliteit, aantal invasieve interventies, kwaliteit van leven, opnameduur, Comprehensive Complication Index, nieuw ontstaan orgaanfalen.

Kennisvraag 2: Leidt een aanvullende percutane drainage tot een sneller klinisch herstel bij patiënten die reeds endoscopisch zijn gedraineerd?

P: Patiënten met geïnfecteerde pancreasnecrose die reeds endoscopische zijn gedraineerd maar die niet voldoende opknappen
I: Aanvullende percutane drainage zo nodig gevolgd door (endoscopische of percutane) necrosectomie
C: Endoscopische necrosectomie
O: Mortaliteit, aantal invasieve interventies, kwaliteit van leven, opnameduur, Comprehensive Complication Index, nieuw ontstaan orgaanfalen.

Implementeren-tabel

Vraag	*Antwoord:* *Kruis aan en licht toe/ beschrijf*		*Toelichting keuze:*
I1. Wat was het onderliggende probleem om deze uitgangsvraag uit te werken?	**x**	**Ongewenste praktijkvariatie**	Grote praktijkvariatie in Nederland
	x	**Nieuwe evidentie**	
		Anders	
I2. Maak een inschatting over hoeveel patiënten het ongeveer gaat waar de aanbeveling betrekking op heeft?	**x**	**< 1000**	
		< 5000	
		5000-40.000	
		> 40.000	
I3. Is de aanbeveling onderdeel van een bredere set interventies of verwant aan andere richtlijnen of modules? Zo ja, hoe verhoudt zij zich daartoe en moet hiermee rekening worden gehouden bij de implementatie, of kan de aanbeveling als losstaand worden beschouwd?	**x**	**Ja**	Verwant aan module – timing drainage
		Nee	
I4. Belemmeringen en kansen op verschillende niveaus voor landelijke toepassing van de aanbeveling:		**Belemmerende factoren**	**Bevorderende factoren/ kansen**
Richtlijn/ klinisch traject (innovatie)		Gebrek aan eenduidig bewijs.	Belangrijkste advies is conform huidig beleid
Zorgverleners (artsen en verpleegkundigen)		-	-
Patiënt/ cliënt (naasten)		-	-
Sociale context		-	-
Organisatorische context		Geïnfecteerde necrotiserende pancreatitis is relatief zeldzaam, kleinere ziekenhuizen zien dit misschien een paar keer per jaar	Endoscopische, interventieradiologische en chirurgische expertise is in Nederland ruim aanwezig < 1 uur reistijd.
Financiële en juridische context			

I5. A) Welke personen/partijen zijn van belang bij het toepassen van de aanbeveling in de praktijk? (kruis aan) **B) Wat is er nodig van deze personen/partijen om de aanbeveling in de praktijk te kunnen brengen?** *Denk aan aanpassingen in gedrag, werkwijzen, beleid, samenwerking of andere randvoorwaarden.*		**A**	**B**
		Patiënt/ cliënt (naaste)	
	x	Professional	
	x	Beroepsvereniging, nl	
		Ziekenhuis (raad van bestuur/UMCNL (voorheen NFU)/NVZ)	
		Zorgverzekeraars/ NZa	
		Zorginstituut [duiding nodig]	
		Anders	
I6. Binnen welk tijdsbestek moet de aanbeveling zijn geïmplementeerd?	**x**	< 1 jaar	
		binnen 2-3 jaar	
I7. Conclusie: is er extra actie en/of ondersteuning nodig voor implementatie van de aanbeveling? *De reguliere implementatieroutes (publicatie en disseminatie via officiele kanalen, opname in professionele standaarden, scholing en nascholing, gebruik van bestaande ICT systemen, audits en visitaties) van de richtlijnmodule alleen is onvoldoende.*	**x**	Ja	Publicatie in Nederlandse vakbladen; NVMDL, NVvH, V&VN, NAPA, NVIR, NVIC, NVMM
		Nee	
I8. Plaatsing op de Landelijke Implementatieagenda Medisch Specialistische zorg is gewenst. *Het gaat om zorg die (grotendeels) wordt uitgevoerd binnen de ziekenhuismuren. Succesvolle implementatie vraagt om actieve betrokkenheid en samenwerking van meerdere relevante partijen binnen de zorgpraktijk.*	**x**	Ja *	
		Nee	

**Deze aanbeveling komt mogelijk in aanmerking voor plaatsing op de Landelijke Implementatieagenda van het programma Zorg Evaluatie & Gepast Gebruik (ZE&GG), waarin alle betrokken partijen in de medisch-specialistische zorg samenwerken aan de implementatie van bewezen beste zorg. De Federatie levert namens het veld goed onderbouwde aanbevelingen aan, die zijn getoetst op de behoefte aan een implementatie-impuls. De onderwerpen op de Implementatieagenda zijn onderdeel van landelijke zorginkoopafspraken tussen zorgverzekeraars en zorgaanbieders. Voor de beoordeling van aanbevelingen uit richtlijnen wordt gebruikgemaakt van de implementatietabel. Op basis hiervan kunnen we de andere partijen goed informeren en gezamenlijk besluiten of plaatsing op de Implementatieagenda passend is.*

Literatuur

Bang JY, Lakhtakia S, Thakkar S, Buxbaum JL, Waxman I, Sutton B, Memon SF, Singh S, Basha J, Singh A, Navaneethan U, Hawes RH, Wilcox CM, Varadarajulu S; United States Pancreatic Disease Study Group. Upfront endoscopic necrosectomy or step-up endoscopic approach for infected necrotising pancreatitis (DESTIN): a single-blinded, multicentre, randomised trial. Lancet Gastroenterol Hepatol. 2024 Jan;9(1):22-33. doi: 10.1016/S2468-1253(23)00331-X. Epub 2023 Nov 18. PMID: 37980922.

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Mohamadnejad M, Hassanzadeh M, Anushirvani A, Sorouri M, Fakhar N, Radmard AR, Mirzaei S, Kasaeian A, Moghtadaie A, Malekzadeh R, Al-Haddad M. Immediate vs On-Demand Endoscopic Necrosectomy in Infected Walled-Off Pancreatic Necrosis: A Randomized Controlled Trial. Clin Gastroenterol Hepatol. 2026 Jun;24(6):1580-1590. doi: 10.1016/j.cgh.2026.02.014. Epub 2026 Feb 19. PMID: 41722664.

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Bijlagen bij module Aanvullende necrosectomie bij Acute Pancreatitis

Risk of Bias tables

Study reference (first author, publication year)	**Was the allocation sequence adequately generated?** Definitely yes Probably yes Probably no Definitely no	**Was the allocation adequately concealed?** Definitely yes Probably yes Probably no Definitely no	**Blinding: Was knowledge of the allocated interventions adequately prevented?** **Were patients blinded?** **Were healthcare providers blinded?** **Were data collectors blinded?** **Were outcome assessors blinded?** **Were data analysts blinded?** Definitely yes Probably yes Probably no Definitely no	**Was loss to follow-up (missing outcome data) infrequent?** Definitely yes Probably yes Probably no Definitely no	**Are reports of the study free of selective outcome reporting?** Definitely yes Probably yes Probably no Definitely no	**Was the study apparently free of other problems that could put it at a risk of bias?** Definitely yes Probably yes Probably no Definitely no	**Overall risk of bias** **If applicable/necessary, per outcome measure** **LOW** **Some concerns** **HIGH**
Bang (2024)	Probably yes Patients were randomly assigned (1:1) by permuted block randomisation	Definitely no No information about allocation concealment	Definitely no Endoscopists were not masked to treatment allocation, but participants, research coordinators, and the statistician were.	Definitely yes	Probably yes No study protocol published in advance, therefore this is not certain.	Probably yes	**High:** mortality, number of reinterventions, length of hospital stay, adverse events

5

Table of excluded studies

Reference	Reason for exclusion
Abdullah A. Al-Shahrani, Benjamin W. Warren, Samuel Han, Steven A. Edmundowicz, Mihir S. Wagh, Sachin B. Wani, Hazem T. Hammad, Augustin R. Attwell, Raj J. Shah. Immediate Direct Endoscopic Necrosectomy Versus Delayed Direct Endoscopic Necrosectomy. Techniques and Innovations in Gastrointestinal Endoscopy. 2024;26(4):306-315. doi: 10.1016/j.tige.2024.06.008.	Wrong study design
Bang JY, Holt BA, Hawes RH, Hasan MK, Arnoletti JP, Christein JD, Wilcox CM, Varadarajulu S. Outcomes after implementing a tailored endoscopic step-up approach to walled-off necrosis in acute pancreatitis. Br J Surg. 2014 Dec;101(13):1729-38. doi: 10.1002/bjs.9664. Epub 2014 Oct 21. PMID: 25333872.	Wrong comparison and two separate time intervals
Baroud S, Chandrasekhara V, Storm AC, Law RJ, Vargas EJ, Levy MJ, Mahmoud T, Bazerbachi F, Bofill-Garcia A, Ghazi R, Maselli DB, Martin JA, Vege SS, Takahashi N, Petersen BT, Topazian MD, Abu Dayyeh BK. A Protocolized Management of Walled-Off Necrosis (WON) Reduces Time to WON Resolution and Improves Outcomes. Clin Gastroenterol Hepatol. 2023 Sep;21(10):2543-2550.e1. doi: 10.1016/j.cgh.2023.04.029. Epub 2023 May 8. PMID: 37164115.	Wrong comparison
Charnley RM, Lochan R, Gray H, O'Sullivan CB, Scott J, Oppong KE. Endoscopic necrosectomy as primary therapy in the management of infected pancreatic necrosis. Endoscopy. 2006 Sep;38(9):925-8. doi: 10.1055/s-2006-944731. PMID: 16981111.	No comparison of interventions
Gardner TB, Chahal P, Papachristou GI, Vege SS, Petersen BT, Gostout CJ, Topazian MD, Takahashi N, Sarr MG, Baron TH. A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. Gastrointest Endosc. 2009 May;69(6):1085-94. doi: 10.1016/j.gie.2008.06.061. Epub 2009 Feb 24. PMID: 19243764.	Wrong study design
Gupta R, Kulkarni AA, Babu R, Shenvi S, Gupta R, Sharma G, Kang M, Sharma V, Singh H, Kumar-M P, Rana S. Predrainage and Postdrainage Prognostic Nomograms to Predict Outcome of Percutaneous Drainage for Infected Pancreatic and Peripancreatic Necrotic Collections. Pancreas. 2019 Oct;48(9):1212-1219. doi: 10.1097/MPA.0000000000001395. PMID: 31593016.	No comparison of interventions
Kumar N, Conwell DL, Thompson CC. Direct endoscopic necrosectomy versus step-up approach for walled-off pancreatic necrosis: comparison of clinical outcome and health care utilization. Pancreas. 2014 Nov;43(8):1334-9. doi: 10.1097/MPA.0000000000000213. PMID: 25083997; PMCID: PMC5019103.	Observational study with no adjustment for confounders
Sato T, Saito T, Takenaka M, Iwashita T, Shiomi H, Fujisawa T, Hayashi N, Iwata K, Maruta A, Mukai T, Masuda A,	Study protocol

Matsubara S, Hamada T, Inoue T, Ohyama H, Kuwatani M, Kamada H, Hashimoto S, Shiratori T, Yamada R, Kogure H, Ogura T, Nakahara K, Doi S, Chinen K, Isayama H, Yasuda I, Nakai Y; WONDERFUL study group in Japan, collaborators. WONDER-01: immediate necrosectomy vs. drainage-oriented step-up approach after endoscopic ultrasound-guided drainage of walled-off necrosis-study protocol for a multicentre randomised controlled trial. Trials. 2023 May 24;24(1):352. doi: 10.1186/s13063-023-07377-y. PMID: 37226252; PMCID: PMC10207852.	
Shenvi S, Gupta R, Kang M, Khullar M, Rana SS, Singh R, Bhasin DK. Timing of surgical intervention in patients of infected necrotizing pancreatitis not responding to percutaneous catheter drainage. Pancreatology. 2016 Sep-Oct;16(5):778-87. doi: 10.1016/j.pan.2016.08.006. Epub 2016 Aug 13. PMID: 27592206.	Wrong comparison
Tsujimae M, Saito T, Sakai A, Takenaka M, Omoto S, Hamada T, Ota S, Shiomi H, Takahashi S, Fujisawa T, Suda K, Matsubara S, Uemura S, Iwashita T, Yoshida K, Maruta A, Okuno M, Iwata K, Hayashi N, Mukai T, Yasuda I, Isayama H, Nakai Y, Masuda A; WONDERFUL study group in Japan. Necrosectomy and its timing in relation to clinical outcomes of EUS-guided treatment of walled-off pancreatic necrosis: a multicenter study. Gastrointest Endosc. 2025 Jun;101(6):1174.e1-1174.e20. doi: 10.1016/j.gie.2024.11.039. Epub 2024 Nov 26. PMID: 39603541.	Wrong comparison
Wu S, Dou X, Li N, Zhu H, Wang L, Liu M, Yu C. Postponed endoscopic necrosectomy results in a lower rate of additional intervention for infected walled-off necrosis. Sci Rep. 2024 May 21;14(1):11610. doi: 10.1038/s41598-024-61675-2. PMID: 38773218; PMCID: PMC11109209.	Wrong comparison
Yan L, Dargan A, Nieto J, Shariaha RZ, Binmoeller KF, Adler DG, DeSimone M, Berzin T, Swahney M, Draganov PV, Yang DJ, Diehl DL, Wang L, Ghulab A, Butt N, Siddiqui AA. Direct endoscopic necrosectomy at the time of transmural stent placement results in earlier resolution of complex walled-off pancreatic necrosis: Results from a large multicenter United States trial. Endosc Ultrasound. 2019 May-Jun;8(3):172-179. doi: 10.4103/eus.eus_108_17. PMID: 29882517; PMCID: PMC6590004.	Observational study with no adjustment for confounders

Literature search strategy

Zoekstrategie Embase.com

No.	*Query*	*Results*
#1	'pancreas necrosis'/exp OR 'acute pancreatitis'/exp OR 'acute hemorrhagic pancreatitis'/exp OR (('pancreatitis'/exp OR pancreatit*:ti,ab,kw OR ((pancrea* NEAR/3 inflammation*):ti,ab,kw)) AND ('necrosis'/de OR acut*:ti,ab,kw OR necroti*:ti,ab,kw OR necros*:ti,ab,kw))	76145

#2	'necrosectomy'/exp OR ((necroti* NEAR/7 (excis* OR exeres* OR remov* OR resect*)):ti,ab,kw) OR necrosect*:ti,ab,kw OR debrid*:ti,ab,kw	55850
#3	#1 AND #2	3386
#4	#3 AND [2005-2025]/py NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'clinical trial':dtype) NOT (('animal'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	1281
#5	'meta analysis'/exp OR 'systematic review'/exp OR 'scoping review'/exp OR 'rapid review'/exp OR 'umbrella review'/exp OR 'cochrane database of systematic reviews'/jt OR 'network meta-analysis'/exp OR 'networkmeta analy*':ti,ab,kw OR 'networkmetaanaly*':ti,ab,kw OR metaanaly*:ti,ab,kw OR 'meta analy*':ti,ab,kw OR metanaly*:ti,ab,kw OR prisma:ti,ab,kw OR prospero:ti,ab,kw OR metaanali*:ti,ab,kw OR 'meta anali*':ti,ab,kw OR metanali*:ti,ab,kw OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab,kw) OR (((structured OR systemic*) NEAR/3 (review* OR overview* OR synth*) NEAR/3 literature):ti,ab,kw) OR ((systemic* NEAR/1 review*):ti,ab,kw) OR (((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab,kw) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab,kw) OR (((literature NEAR/3 (review* OR overview*)):ti,ab,kw) AND (search*:ti,ab,kw OR database*:ti,ab,kw OR 'data base*':ti,ab,kw)) OR (('data extraction*':ti,ab,kw OR 'data source*':ti,ab,kw) AND ('study selection*':ti,ab,kw OR 'studies selection*':ti,ab,kw)) OR ('search strateg*':ti,ab,kw AND 'selection criteria*':ti,ab,kw) OR ('data source*':ti,ab,kw AND 'data synth*':ti,ab,kw) OR medline*:ti,ab,kw OR pubmed*:ti,ab,kw OR 'pub med*':ti,ab,kw OR embase:ti,ab,kw OR cochrane*:ti,ab,kw OR (((critical* OR rapid*) NEAR/2 (review* OR overview* OR synth*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synth*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynth*:ti,ab,kw OR 'meta synth*':ti,ab,kw OR 'review* of review*':ti,ab,kw	1137375
#6	'clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti	4850827
#7	'major clinical study'/de OR 'clinical study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'cohort analysis'/de OR 'case control study'/de OR 'comparative study'/exp OR 'control group'/de OR 'controlled study'/de OR 'controlled clinical trial'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'pretest posttest design'/de OR 'pretest posttest control group design'/de OR 'quasi experimental study'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR	18777854

	studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti) OR (((control OR controlled) NEAR/6 trial):ti,ab,kw) OR (((control OR controlled) NEAR/6 (study OR studies)):ti,ab,kw) OR (((control OR controlled) NEAR/1 active):ti,ab,kw) OR 'open label*':ti,ab,kw OR (((double OR two OR three OR multi OR trial) NEAR/1 (arm OR arms)):ti,ab,kw) OR ((allocat* NEAR/10 (arm OR arms)):ti,ab,kw) OR placebo*:ti,ab,kw OR 'sham-control*':ti,ab,kw OR (((single OR double OR triple OR assessor) NEAR/1 (blind* OR masked)):ti,ab,kw) OR nonrandom*:ti,ab,kw OR 'non-random*':ti,ab,kw OR 'quasi-experiment*':ti,ab,kw OR crossover:ti,ab,kw OR 'cross over':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'factorial trial':ti,ab,kw OR ((phase NEAR/5 (study OR trial)):ti,ab,kw) OR ((case* NEAR/6 (matched OR control*)):ti,ab,kw) OR ((match* NEAR/6 (pair OR pairs OR cohort* OR control* OR group* OR healthy OR age OR sex OR gender OR patient* OR subject* OR participant*)):ti,ab,kw) OR ((propensity NEAR/6 (scor* OR match*)):ti,ab,kw) OR versus:ti OR vs:ti OR compar*:ti OR ((compar* NEAR/1 study):ti,ab,kw) OR (('observational study'/de OR 'cross-sectional study'/de OR 'multicenter study'/de OR 'correlational study'/de OR 'follow up'/de OR cohort*:ti,ab,kw OR 'follow up':ti,ab,kw OR followup:ti,ab,kw OR longitudinal*:ti,ab,kw OR prospective*:ti,ab,kw OR retrospective*:ti,ab,kw OR observational*:ti,ab,kw OR 'cross sectional*':ti,ab,kw OR cross?ectional*:ti,ab,kw OR multicent*:ti,ab,kw OR 'multi-cent*':ti,ab,kw OR consecutive*:ti,ab,kw) AND (group:ti,ab,kw OR groups:ti,ab,kw OR subgroup*:ti,ab,kw OR versus:ti,ab,kw OR vs:ti,ab,kw OR compar*:ti,ab,kw OR 'odds ratio*':ab OR 'relative odds':ab OR 'risk ratio*':ab OR 'relative risk*':ab OR 'rate ratio':ab OR aor:ab OR arr:ab OR rrr:ab OR ((('or' OR 'rr') NEAR/6 ci):ab)))	
#8	#4 AND #5 - SR	73
#9	#4 AND #6 NOT #8 - RCT	178
#10	#4 AND #7 NOT (#8 OR #9) - Observationeel	458
#11	#8 OR #9 OR #10 - Totaal	709

Zoekstrategie Ovid/Medline

#	Searches	Results
1	exp Pancreatitis, Acute Hemorrhagic/ or exp Pancreatitis, Acute Necrotizing/ or ((exp Pancreatitis/ or pancreatit*.ti,ab,kf. or (pancrea* adj3 inflammation*).ti,ab,kf.) and (exp Acute Disease/ or Necrosis/ or acut*.ti,ab,kf. or necroti*.ti,ab,kf. or necros*.ti,ab,kf.))	43456
2	((necroti* adj7 (excis* or exeres* or remov* or resect*)) or necrosect* or debrid*).ti,ab,kf.	42368
3	1 and 2	1560
4	limit 3 to yr="2005 -Current"	1144
5	4 not (comment/ or editorial/ or letter/) not ((exp animals/ or exp models, animal/) not humans/)	1088
6	exp Meta-Analysis/ or exp Network Meta-Analysis/ or exp Systematic Review/ or (networkmeta analy* or networkmetaanaly* or metaanaly* or meta analy* or	844196

	metanaly* or prisma or prospero or metaanali* or meta anali* or metanali*).ti,ab,kf. or ((systemati* or scoping or umbrella or structured literature) adj3 (review* or overview*)).ti,ab,kf. or ((structured or systemic*) adj3 (review* or overview* or synth*) adj3 literature).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 (review* or overview*)) and (search* or database* or data base*)).ti,ab,kf. or ((data extraction* or data source*) and (study selection* or studies selection*)).ti,ab,kf. or (search strateg* and selection criteria*).ti,ab,kf. or (data source* and data synth*).ti,ab,kf. or (medline* or pubmed* or pub med* or embase or cochrane*).ti,ab,kf. or cochrane.jw. or ((critical* or rapid*) adj2 (review* or overview* or synth*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synth*)) and (search* or database* or data base*)).ab. or metasynth*.ti,ab,kf. or meta synth*.ti,ab,kf.	
7	exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.	2915201
8	Case-control Studies/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or comparative study/ or control groups/ or controlled before-after studies/ or controlled clinical trial/ or double-blind method/ or historically controlled study/ or matched-pair analysis/ or single-blind method/ or (((control or controlled) adj6 (study or studies or trial)) or (compar* adj (study or studies)) or ((control or controlled) adj1 active) or "open label*" or ((double or two or three or multi or trial) adj (arm or arms)) or (allocat* adj10 (arm or arms)) or placebo* or "sham-control*" or ((single or double or triple or assessor) adj1 (blind* or masked)) or nonrandom* or "non-random*" or "quasi-experiment*" or "parallel group*" or "factorial trial" or "pretest posttest" or (phase adj5 (study or trial)) or (case* adj6 (matched or control*)) or (match* adj6 (pair or pairs or cohort* or control* or group* or healthy or age or sex or gender or patient* or subject* or participant*)) or (propensity adj6 (scor* or match*))).ti,ab,kf. or (confounding adj6 adjust*).ti,ab. or (versus or vs or compar*).ti. or exp cohort studies/ or epidemiologic studies/ or ((multicenter study/ or observational study/ or seroepidemiologic studies/ or (cohort* or 'follow up' or followup or longitudinal* or prospective* or retrospective* or observational* or multicent* or 'multi-cent*' or consecutive*).ti,ab,kf.) and ((group or groups or subgroup* or versus or vs or compar*).ti,ab,kf. or ('odds ratio*' or 'relative odds' or 'risk ratio*' or 'relative risk*' or aor or arr or rrr).ab. or (("OR" or "RR") adj6 CI).ab.)) or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/	8097643
9	5 and 6 - SR	59
10	(5 and 7) not 9 - RCT	115
11	(5 and 8) not (9 or 10) - Observationeel	418
12	9 or 10 or 11 - Totaal	592