GUIDELINES

Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document

S A Khan, B R Davidson, R Goldin, S P Pereira, W M C Rosenberg, S D Taylor-Robinson, A V Thillainayagam, H C Thomas, M R Thursz, H Wasan

1.0 GUIDELINES

1.1 Development of guidelines

There is currently no clear national consensus for the optimal diagnosis and treatment of cholangiocarcinoma. The need for these guidelines was highlighted following the annual meeting of the British Association for the Study of the Liver (BASL) in September 2000. During their development these guidelines were presented at a BASL Liver Cancer Workshop in January 2001. They were also circulated to BASL members and the Liver Section of the British Society of Gastroenterology (BSG) Committee members, including gastroenterologists, hepatologists, gastroenterological surgeons, pathologists, radiologists, and epidemiologists for comments before the final consensus document was drawn up.

1.2 Strategy

The guidelines are based on comprehensive literature surveys including results from randomised controlled trials, systematic reviews and meta-analyses, and cohort, prospective, and retrospective studies. On issues where no significant study data were available, evidence was obtained from expert committee reports or opinions. Where possible, specific recommendations have been graded, based on the quality of evidence available (section 2.4).

1.3 Context and intent

These guidelines are intended to bring consistency and improvement in the patient’s management from first suspicion of cholangiocarcinoma through to confirmation of the diagnosis and subsequent management. As stated in previous BSG guidelines, patient preferences must be sought and decisions made jointly by the patient and health carer, based on the risks and benefits of any intervention.

Furthermore, the guidelines should not necessarily be regarded as the standard of care for all patients. Individual cases must be managed on the basis of all clinical data available for that case. The guidelines are subject to change in light of future advances in scientific knowledge.

2.0 BACKGROUND

Mortality rates from intrahepatic cholangiocarcinoma have risen steeply and steadily over the past 30 years and since the mid 1990s more deaths have been coded annually in England and Wales as being due to this tumour than to hepatocellular carcinoma. In 1997 and 1998 cholangiocarcinoma caused almost 1000 deaths/year in England and Wales (approximately equal numbers of men and women). The cause of this rise is unknown and does not appear to be explained simply by improvements in diagnosis or changes in coding practice. The incidence of biliary cancers corresponds to mortality rates as the prognosis from these tumours is very poor.

2.1 Risk factors

- Age (65% of patients are over 65 years old).
- Primary sclerosing cholangitis (PSC), with or without ulcerative colitis, is the commonest known predisposing factor for cholangiocarcinoma in the UK (lifetime risk 5–15%).
- Chronic intraductal gall stones.
- Bile duct adenoma and biliary papillomatosis.
- Caroli’s disease (cystic dilatation of ducts, lifetime risk 7%).
- Choledochal cysts (about 5% will transform, risk increases with age).
- Thorotrast (a radiological agent no longer licensed for use, although the risk of cholangiocarcinoma lasts several decades).
- Smoking (increased risk in association with PSC).
- In SE Asia, where the tumour is quite common, the associated risk factors are:
  - liver flukes—Opisthorchis viverrini and Clonorchis sinensis,
  - chronic typhoid carriers—sixfold increased risk of all hepatobiliary malignancy.

2.2 Anatomical classification

“Cholangiocarcinoma” originally referred only to primary tumours of the intrahepatic bile ducts and was not used for extrahepatic bile duct tumours but the term is now regarded as inclusive of intrahepatic, perihilar, and distal extrahepatic tumours of the bile ducts (fig 1).

- 20–25% are intrahepatic.
- 50–60% of all cases of cholangiocarcinoma are perihilar tumours (those involving the bifurcation of the ducts are “Klatskin” tumours).
- Most Klatskin tumours may have been coded as intrahepatic tumours for purposes of death certification.
- 20–25% are distal extrahepatic tumours.
- About 5% of tumours may be multifocal.
- The extent of duct involvement by perihilar tumours may be classified as suggested by Bismuth:
  - type I: tumours below the confluence of the left and right hepatic ducts;
  - type II: tumours reaching the confluence but not involving the left or right hepatic ducts;

Abbreviations: BASL, British Association for the Study of the Liver; BSG, British Society of Gastroenterology; PSC, primary sclerosing cholangitis; CEA, carcinoembryonic antigen; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, MR cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography; TNM, tumour-node-metastasis; LDH, lactate dehydrogenase; 5-FU, 5-fluorouracil.
Most cholangiocarcinomas (95%) are adenocarcinomas. Adenocarcinomas are classified (1–4) according to the percentage of tumour that is composed of glandular tissue. Some types of adenocarcinoma are however not graded: carcinoma in situ, clear cell adenocarcinoma, and papillary adenocarcinoma. Signet ring cell carcinoma is given a grade of 3 and small cell carcinoma a grade of 4. Squamous cell carcinomas are graded according to the least differentiated areas. Most studies have demonstrated a relation between histological grade and post-operative outcome although stage is more important.

2.3.4 Molecular diagnosis
- Cholangiocarcinoma is often associated with inactivation of tumour suppressor genes—for example, p53, APC, Smad-4, bcl-2, and p16.
- Mutations in oncogenes have also been described—for example, K-ras, c-myc, c-erbB-2, and c-neu.
- Chromosomal aneuploidy has been reported in up to 25% of peripancreatic tumours.
- Although these mutations can lead to detectable phenotypic changes, the diagnostic or prognostic usefulness of these developments is unclear and molecular profiling does not, as yet, have an established clinical role in patients with cholangiocarcinoma.

2.4 Levels of evidence
Studies used as a basis for these guidelines are graded in relation to the quality of evidence according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). These are summarised in the appendix with explanatory notes, and have been reproduced with the permission of the Centre for Evidence-based Medicine.

3.0 DIAGNOSIS
3.1 Clinical features
- Most common presenting clinical features of perihilar or extrahepatic tumours are those of biliary obstruction: jaundice, pale stool, dark urine, and pruritus.
- Right upper quadrant pain, fever, and rigors suggest cholangitis (this is unusual without drainage attempts).
- Cholangiocarcinoma usually presents after the disease is advanced. This is particularly true with more proximal intrahepatic and perihilar tumours obstructing one duct, which often present with systemic manifestations of malignancy, such as malaise, fatigue, and weight loss.
- Some cases are detected incidentally as a result of deranged liver function tests, or ultrasound scans performed for other indications.

3.2 Blood tests
There are no blood tests diagnostic for cholangiocarcinoma. Liver function tests often show an obstructive picture with raised:
- alkaline phosphatase
- bilirubin
- gamma glutamyl transpeptidase.

However, aminotransferases are frequently relatively normal but may be markedly raised in acute obstruction or cholangitis.
- Prolonged obstruction of the common bile or hepatic duct can cause a reduction in fat soluble vitamins (A, D, E, and K) and increase prothrombin time.
Intrahepatic cholangiocarcinoma may be seen as a mass.

Diagnosis should be suspected when intrahepatic, but not extrahepatic, ducts are dilated.

Intrahepatic cholangiocarcinoma may be seen as a mass lesion but this is unusual.

Other serum tumour markers
Several other potential serum tumour markers have been linked to cholangiocarcinoma including CA-195, CA-242, DU-PAN-2, IL-6, and trypsinogen-2. Their clinical role is currently unclear.

CA 19-9
The value of CA 19-9 in patients with suspected cholangiocarcinoma is unclear. However:
- It is raised in up to 85% of patients with cholangiocarcinoma;
- it has been reported that a CA 19-9 value greater than 100 U/ml has a sensitivity of 75% and specificity of 80% in patients with PSC;
- CA 19-9 elevation can occur in obstructive jaundice without malignancy but persistently raised levels of CA 19-9 after biliary decompression suggest malignancy;
- CA 19-9 does not discriminate between cholangiocarcinoma, pancreatic, or gastric malignancy and may also be elevated in severe hepatic injury from any cause;
- the value of CA 19-9 for detecting cholangiocarcinoma in patients without PSC is unknown;
- CA 19-9 may be useful for the differential diagnosis of cholangiocarcinoma but further studies are needed.

CEA
Carcinoembryonic antigen (CEA) is raised in approximately 30% of patients with cholangiocarcinoma.

CEA can also be elevated in inflammatory bowel disease, biliary obstruction, other tumours, and severe liver injury.

CA-125
This is elevated in 40–50% of cholangiocarcinoma patients.

It may signify the presence of peritoneal involvement but further studies are needed.

Other serum tumour markers
Several other potential serum tumour markers have been linked to cholangiocarcinoma including CA-195, CA-242, DU-PAN-2, IL-6, and trypsinogen-2. Their clinical role is currently unclear.

3.3 Imaging

3.3.1 Ultrasonography (US)
Remains the first-line investigation for suspected biliary obstruction.

Diagnosis should be suspected when intrahepatic, but not extrahepatic, ducts are dilated.

Intrahepatic cholangiocarcinoma may be seen as a mass lesion but this is unusual.

• As the sensitivity and specificity of individual tumour markers is low, patients should have a combination of serum tumour markers measured where diagnostic doubt exists. However, diagnosis should not rest solely on serum tumour marker measurements (recommendation grade C).

With advanced disease, systemic non-specific markers of malignancy may be altered—for example, reduced albumin, haemoglobin, and lactate dehydrogenase (LDH).

3.3.2 Computed tomography (CT)
CT may provide good views of intrahepatic mass lesion, dilated intrahepatic ducts, and localised lymphadenopathy, however:
- CT does not usually define the extent of cholangiocarcinoma,
- abdominal lymphadenopathy is common in PSC and does not necessarily indicate malignant change,
- suspected perihilar tumours or those involving the portal venous/arterial system should be studied by contrast enhanced spiral/helical CT.

3.3.3 Magnetic resonance imaging (MRI)
At present good quality MR is the optimal initial investigation for suspected cholangiocarcinoma, providing information on:
- liver and biliary anatomy and local extent of the tumour,
- extent of duct involvement by tumour with MR cholangiopancreatography (MRCP),
- hepatic parenchymal abnormalities and presence of liver metastases,
- hilar vascular involvement by MR angiography.

3.3.4 Cholangiography (MRCP, ERCP, and PTC)
Essential for early diagnosis of cholangiocarcinoma and assessing resectability.

MRCP is non-invasive and determines the extent of cholangiocarcinoma, pancreatic, or gastric malignancy and may also be useful for monitoring tumour progression. CA 19-9, carcinoembryonic antigen (CEA), and CA-125 are currently the most widely used serum tumour markers.

Recommendations
- As the sensitivity and specificity of individual tumour markers is low, patients should have a combination of serum tumour markers measured where diagnostic doubt exists. However, diagnosis should not rest solely on serum tumour marker measurements (recommendation grade C).

• Gall stones excluded.
• Often misses small perihilar, extrahepatic, and peripancreatic tumours and not good at defining the extent of the tumour.
• Colour Doppler can detect tumour induced compression/thrombosis of the portal vein or hepatic artery.

3.3.5 New techniques
There are several new promising techniques that are under evaluation.

Endoscopic ultrasound
- Allows good view of distal extrahepatic biliary tree, gall bladder, regional lymph nodes, and vasculature.
Obtain at ERCP, they are recommended for confirmation of a diagnosis of cholangiocarcinoma. Histology is also important for planning clinical trials. An adenocarcinoma is the usual histological subtype seen (see section 2.3.3 above). The only histological feature that allows a definite diagnosis of cholangiocarcinoma to be made is the presence of coexisting carcinoma in situ and this is uncommon. However, for patients with potentially curable (resectable) disease, open or percutaneous biopsy is not recommended due to the risk of tumour seeding.

3.5 Excluding metastatic disease

Cholangiocarcinoma is sometimes very difficult to differentiate from metastatic adenocarcinoma, particularly if the pathological diagnosis is obtained from outside the biliary tree—for example, porta hepatitis lymph node/mass or from liver metastases. Thorough clinical examination and other investigations are necessary to exclude a primary from elsewhere. The extent to which another possible primary is pursued and investigations done (some suggested below) will depend on the clinical situation in each individual case. Metastatic adenocarcinoma mimicking cholangiocarcinoma may arise from several organs, particularly:

1. pancreas—axial imaging (for example, MR, CT, EUS) (evidence levels 2b, 3a; recommendation grade B);
2. stomach—axial imaging, endoscopy (evidence levels 2b, 3a; recommendation grade B);
3. breast—clinical examination, mammography only if breast mass (evidence level 1b; recommendation grade A);
4. lung—chest radiography (evidence levels 2b, 3a; recommendation grade B);
5. colon—colonoscopy or spiral CT (evidence level 3a; recommendation grade B).

Serum tumour markers may also be useful—for example, LDH, α-fetoprotein (evidence level 3b; recommendation grade B).

4.0 TREATMENT

4.1 Surgery

Surgery is the only curative treatment for patients with cholangiocarcinoma. Surgery cures the minority of patients with cholangiocarcinoma, with a 9–18% five year survival for proximal bile duct lesions and 20–30% for distal lesions.

- Bile duct cancers may be multifocal (5%).
- Lymph node involvement is present in 50% of all patients at presentation and is associated with poor surgical outcome.
- Peritoneal and distant metastases are present in 10–20% of all patients at presentation.

4.1.1 Resectable tumours

- Patients’ suitability for major surgery should be guided by medical risk factors rather than age.
Irradiation (for example, brachytherapy or external beam radiation therapy, unproved in cholangiocarcinoma).

Intraoperative coeliac plexus block for pain control (unproved in cholangiocarcinoma).

Close liaison between oncological and surgical teams is important.

4.1.2 Liver transplantation for unresectable tumours

Liver transplantation is currently contraindicated (recommendation grade B)

- It is usually associated with rapid recurrence of disease and death within three years.
- In pilot studies, liver transplantation following preoperative chemoradiation for unresectable cholangiocarcinoma has resulted in long term survival of carefully selected patients and may be appropriate within clinical trials.

4.1.3 Palliative procedures

- Surgical resection with palliative, rather than curative, intent is unproved.
- Symptoms related to biliary obstruction in unresectable disease may be palliated by insertion of a biliary endoprosthesis (see below) rather than a surgical bypass. Stenting procedures resulting in adequate biliary drainage improves survival. Surgical bypass has not been demonstrated to be superior to stenting.
- Irradiation (for example, brachytherapy or external beam radiation therapy, unproved in cholangiocarcinoma).
- Intraoperative coeliac plexus block for pain control (unproved in cholangiocarcinoma).

The intrahepatic variant of cholangiocarcinoma is treated by resection of the involved segments or lobe of the liver.

Resection involves a major operative procedure and requires appropriate surgical and anaesthetic experience.

Inadequate biliary drainage may increase the risk of sepsis and therefore surgery.

Surgical treatment principally depends on the site and extent of bile duct involvement by the tumour. Survival depends on stage with tumour free margins with the absence of lymphadenopathy being the most important positive prognostic indicator.

Median survival for patients with intrahepatic cholangiocarcinoma:
- without hilar involvement is 18–30 months;
- with perihilar tumour is 12–24 months;
- five year survival rates of up to 40% have been reported for intrahepatic cholangiocarcinoma (best results in Japan), and 20% for hilar cholangiocarcinoma.

Reported five year survival for distal extrahepatic cholangiocarcinoma is currently 20–30%.

4.1.4 Reporting surgical specimens

All surgical resection specimens from both intrahepatic and extrahepatic cholangiocarcinomas need to be reported in a systematic manner. The following information should be included in the final report (recommendation grade D):

(i) Tumour
- histological type (see section 1.3),
- histological grade (see section 1.3),
- extent of invasion (according to the TNM system),
- blood/lymphatic vessel invasion,
- perineural invasion: this is very common and has been shown to be associated with a worse outcome. It is also very useful in making the diagnosis of invasive cancer.

(ii) Margins
- These must be adequately sampled because it has been shown that local recurrence is related to involvement of the margins. This is particularly important because extrahepatic cholangiocarcinomas may be multifocal (5%).

(iii) Regional lymph nodes
- To stage the lymph nodes accurately, the lymph node groups must be specifically identified. It should be noted that peripancreatic nodes located along the body and tail of the pancreas are considered sites of distant metastasis.

(iv) Additional pathological findings
- These must be noted if present—for example, carcinoma in situ, sclerosing cholangitis.

(v) Metastases
- To other organs or structures.

4.2 Biliary decompression and stents

4.2.1 Stenting prior to surgery

- Stents ideally should not be inserted prior to assessing resectability.

- Although the routine use of preoperative biliary drainage is not recommended, in certain patients who are severely malnourished, or who are suffering from acute suppurative cholangitis, preoperative drainage may be beneficial.

- Preoperative placement of biliary catheters may be a useful technical aid in patients requiring a difficult hilar dissection for proximal biliary diseases.

4.2.2 Stents alone for palliation of jaundice

- Stents are used to maintain adequate biliary drainage and relieve symptoms.

- Most stents are inserted endoscopically and are initially plastic.

- The use of MRCP to plan endoscopic stent placement in complex hilar tumours may reduce the risk of postprocedure cholangitis.

- In patients with complex hilar lesions, retrospective case control studies suggest that bilateral versus unilateral
endoscopic/percutaneous biliary drainage may result in improved jaundice, postprocedure cholangitis, and survival, although this was not confirmed in a recent randomised trial.

4.2.3 Complications of stenting

• Complications of endoscopy.

• It should be noted that following palliative stenting, patients can die from recurrent sepsis, biliary obstruction, and stent occlusion as well as disease progression.

4.3 Oncological approaches (evidence levels 2–4)

Surgery is the only curative treatment for patients with cholangiocarcinoma but it is only effective in a minority of cases. At presentation, half of all cholangiocarcinomas have lymph node metastases. Thus successful non-surgical oncological approaches could have a significant beneficial impact on this disease, on the majority of patients if efficacy could be demonstrated. However, to date, the level of evidence for the majority of published studies is 2a or less.

• To date, a review of over 65 disparate studies using chemotherapy and/or radiation suggests that there was no strong evidence of survival benefit. However, most studies were small, lacked control groups (phase II), and were difficult to interpret, particularly as radiological responses for cholangiocarcinoma are not easy to document.

• As a general guide from published trials:
  - (i) patients who are relatively healthy, stable, and not deteriorating rapidly should be treated early in their course of disease rather than wait for their disease to progress. The performance status is generally the most important prognostic factor (patients with a Karnofsky status of 50 or more that are not rapidly deteriorating are usually suitable);
  - (ii) good symptom control is paramount throughout and requires multidisciplinary team input;
  - (iii) in those patients on treatment in whom quality of life is preserved or improved, a survival benefit is more likely. Thus quality of life should probably be the primary focus and survival a secondary end point in disease management;
  - (iv) achieving stable disease (or lack of objective progression) in patients on therapy has value that can be translated into both length and quality of life, and so should not be underestimated as a surrogate end point. This is particularly important because of the frequent difficulty in confirming objective radiological responses, particularly in the perihilar area.

Trial approaches may involve chemotherapy, radiotherapy (external beam, intraoperative, intraluminal brachytherapy), or combinations of the above with or without surgery. Presurgical approaches attempting down staging are classified as “neoadjuvant” and immediately postsurgical as “adjuvant”.

4.3.1 Chemotherapy

• In advanced disease, one randomised study of combination chemotherapy versus best supportive care reported a significantly improved survival (four months of benefit) and quality of life to the chemotherapy arm. (The study also included pancreatic cancers with a positive result although the analysis was separate.)

• There is currently no evidence to support postsurgical adjuvant therapy outside a trial setting.

• Conclusions from predominately phase II studies suggest:
  - (i) cholangiocarcinomas are relatively chemosensitive, with most studies being 5-fluorouracil (5-FU) based, and 10–20% partial response rates to (older) single agents;
  - (ii) partial response rates to newer single agents, such as gemcitabine, vary from 20% to 30%;
  - (iii) partial response rates to recent phase II combinations vary from 20 to 40%.

• Gemcitabine in combination with cisplatin shows 30–50% partial response rates. It is encouraging that several patients have been clearly documented as being down staged and converted to operability in some phase II studies, with occasional long term survivors.

• the chance of responding appears to be correlated with performance status at the outset. Quality of life is significantly improved, particularly in responders.

Currently, a European study of infusional 5-FU with cisplatin compared with infusional 5-FU (EORTC-GITCCG randomised phase II) is recruiting. Oral 5-FU analogues are also now available (UFT-tegafur or capecitabine).

Targeted chemotherapy through the hepatic artery or portal vein has been shown to achieve greater local drug concentrations and improved response rates (44% in one phase II study) but because of the patterns of relapse, it is unlikely to replace systemic chemotherapy entirely.

4.3.2 Radiotherapy

• There is currently no evidence to support adjuvant postoperative radiation therapy. Radiotherapy did not improve survival or the quality of life in patients with resected perihilar cholangiocarcinoma when assessed prospectively.

• There is no evidence for radiotherapy improving survival or the quality of life in advanced disease. There is significant toxicity from current methods of delivery and no evidence of disease sterilising effects without significant morbidity.

• The role of chemoradiation (chemotherapy combined with local radiation) remains to be established in randomised clinical trials as local and systemic toxicity is also concomitantly increased.

• Radiation alone still has potential important palliative value for painful localisable metastases, uncontrolled bleeding, etc.
### Recommendations

- All patients who have inoperable tumours, or who are operable but have not been rendered disease free, or those patients with recurrences should be actively encouraged to participate in chemotherapy and/or radiotherapy clinical trials (recommendation grade B).

### (b) Local radiation techniques: intraoperative or intraluminal brachytherapy

- A few uncontrolled studies using intraluminal brachytherapy (iridium implants), combined with external beam irradiation, have suggested a benefit. In one study, median survival rates reached about 10 months compared with seven months in patients managed by stenting alone.
- Median survival using a combination of external beam irradiation, transcatheter iridium, and chemotherapy (fluorouracil) was 13 months in another uncontrolled study.
- In advanced disease, liver and abdominal cavity relapse were the major causes of progression in these and other radiotherapy studies.

![Management algorithm for cholangiocarcinoma](image)

**Figure 2** Management algorithm for cholangiocarcinoma. US, ultrasonography; MRCP, MR cholangiopancreatography; MRA, MR angiography; ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography. *Where magnetic resonance imaging/MRCP is not possible, patients should have contrast enhanced spiral/helical computed tomography.* **Fine needle biopsy or biopsy is ideally avoided until resectability has been assessed by a specialist surgeon.**

Thus although intraoperative radiotherapy and intraluminal brachytherapy appear promising, the studies do not support their use in isolation and there are no controlled data confirming their value in comparison with standard chemotherapy, chemoradiation, or stenting alone.

### Oncology conclusion

Definitive evidence from large randomised studies for a survival benefit of non-surgical oncological intervention compared with best supportive care is still lacking. Patients with advanced cholangiocarcinoma should therefore be actively offered the opportunity to participate in clinical trials as there are many fewer promising agents and combinations with potential improved efficacy and tolerability. In chemotherapy trials, good performance status patients appear to have the most significant benefit in terms of quality of life.

### 4.4 Recurrent bile duct cancer

The prognosis for any treated patient with progressing, recurring, or relapsing bile duct cancer is poor. Further treatment depends on several factors, including prior treatment and site of recurrence, as well as individual patient considerations. Relief of recurrent jaundice usually improves quality of life. Clinical trials, of chemotherapy in particular, may be appropriate and should be considered when possible.

A management algorithm for cholangiocarcinoma is shown in fig 2.

### 5.0 REVISION OF GUIDELINES

We recommend that these guidelines are regularly audited and we request feedback from all users. These guidelines should be formally revised within three years of publication or sooner in light of new evidence.

### 6.0 APPENDIX: LEVELS OF EVIDENCE

Levels of evidence are shown in table A1.

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### 7.0 REFERENCES

**Table A1** Levels of evidence

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<th>Level</th>
<th>Therapy/prevention</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>DDX/symptom prevalence study</th>
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<td>SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations</td>
<td>SR (with homogeneity*) of level 1 diagnostic studies; CDR† with 1b studies from different clinical centres</td>
<td>SR (with homogeneity*) of prospective cohort studies</td>
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<td>Individual RCT (with narrow confidence interval)</td>
<td>Individual inception cohort study with &gt;80% follow up; CDR† validated in a single population</td>
<td>Validating ** cohort study with good††† reference standards; or CDR† tested within one clinical centre</td>
<td>Prospective cohort study with good follow up****</td>
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<td>All or none case series</td>
<td>Absolute SpPins and SnNouts††</td>
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<td>SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs</td>
<td>SR (with homogeneity*) of level &gt;2 diagnostic studies</td>
<td>SR (with homogeneity*) of 2b and better studies</td>
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<td>Retrospective cohort study or follow up of untreated control patients in an RCT; Derivation of CDR† or validated on split sample§§ only</td>
<td>Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split sample§§ or databases</td>
<td>Retrospective cohort study or poor follow up</td>
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<td>Case series (and poor quality cohort and case control studies§§)</td>
<td>Case series (and poor quality diagnostic studies***): expert opinion without explicit critical appraisal, or based on physiology, bench research, or “first principles”</td>
<td>Case control study; poor or non-independent reference standard</td>
<td>Case series or superseded reference standards</td>
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*Homogeneity means a systematic review (SR) that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all SRs with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant.

§§Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it.

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

†††An “Absolute SpPin”: a diagnostic finding whose specificity is so high that a Positive result rules in the diagnosis. An “Absolute SnNout”: a diagnostic finding whose Sensitivity is so high that a Negative result rules out the diagnosis.

**Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (for example, using a regression analysis) to find which factors are “significant” **Poor quality diagnostic cohort study: one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.

***Good follow p in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge [for example, 1–6 months acute, 1–5 years chronic].
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