

VOLUME I · PARTS 1-4

212

QUESTIONS SOLVED

103

MODEL ANSWERS

12

EXAM SESSIONS

Jun 2020 – Dec 2025

HR bpm

72

SpO2

98

RR

16

EtCO2

35

TEMP °C

36.8

FOR THE DNB GENERAL MEDICINE THEORY EXAMINATION

DNB General Medicine

Solved Previous-Year Questions

VOLUME I

Parts 1-4 · 212 questions · 103 model answers

THE COMPLETE SET · 4 VOLUMES · 863 QUESTIONS · 430 MODEL ANSWERS

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Profession of Medicine, Cardinal Manifestations, Oncology & Hematology, Infectious Diseases

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CLINICA
PUBLICATION

STUDY NOTES

DNB General Medicine

Solved Previous-Year Questions

VOLUME I

Part 1 · The Profession of Medicine

Part 2 · Cardinal Manifestations and Presentation of Diseases

Part 3 · Oncology and Hematology

Part 4 · Infectious Diseases (continued in next volume)

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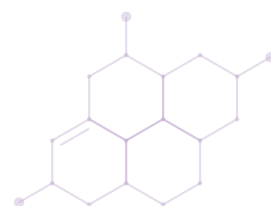
Dr Abhishek Kumar

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Answers are written from Harrison's Principles of Internal Medicine (22nd ed.), with the chapter and printed pages given at the start of each answer, and from current Indian and international guidelines found on official government, society and journal sites, cited [W#] and listed in the Web-Sourced Facts Register.

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HOW TO USE

Each answer groups every year the question was asked and is written to the most demanding version. Badges show how often a topic was asked. Each answer opens with one SOURCE line: the Harrison's 22e chapter and printed pages used, and the guideline/web sources [W#]. The amber Management-basis strip names the guideline versions used (Indian first). Every [W#] is also listed in the register at the end. Section B lists this volume question by question; C lists the high-yield topics of the whole book (asked 3× or more), with volume and page.

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PART I

The Profession of Medicine

1. Statistical analysis in research and Bayes' theorem in diagnosis

ASKED 2* · Intermediate answer

Asked in: Jun 2021 P-IV Q3(a) (5 marks) · May 2024 P-IV Q10(a) (5 marks)

Q: Importance of statistical analysis in research. [5]

Q: How does Bayes' rule help in diagnostic probability? [5]

SOURCE Harrison's 22e — Ch 4 Decision-Making in Clinical Medicine, §Measures of Disease Probability and Bayes' Rule; Applications to Diagnostic Testing in CAD; Risk Prediction Models — pp. 24–26
Harrison's 22e — Ch 8 The Value of the Physical Examination in Modern Medicine — p. 48

Definition

- **Statistical analysis** is the quantitative handling of data that lets a researcher or clinician measure how well a test or model performs, express the remaining uncertainty, and decide whether a result can be trusted.
- **Bayes' rule** quantifies the revised uncertainty after a test. It uses simple probability mathematics, which also helps avoid anchoring bias.
- It calculates the **posttest probability** (likelihood of disease after a test result) from three parameters:
 - pretest probability
 - test sensitivity
 - test specificity
- Both questions rest on one idea: no test is perfect, so the true disease state stays uncertain after every test.

Importance of statistical analysis in research

- **Measures test accuracy objectively.** Sensitivity, specificity and their complements (false-positive and false-negative rates) are calculated against a gold standard.
- **Defines the cut point.** Raising the threshold lowers sensitivity and raises specificity. Lowering it does the opposite.
- **Displays the trade-off with an ROC curve.** Sensitivity is plotted against 1 – specificity, and each point is a possible cut point.
- **Quantifies information content.** The area under the ROC curve runs from **0.5** (no information, like flipping a coin) to **1.0** (perfect test).
- **Guides rational choice of cut point.** It should reflect the relative harms and benefits of treating those with and without disease.
 - Safe treatment with large benefit favours a high-sensitivity cut point (e.g., phenylketonuria in newborns).
 - Risky treatment favours a high-specificity cut point (e.g., chemotherapy for cancer).
- **Accounts for prevalence.** Low prevalence puts more weight on the harms of false-positive tests (e.g., HIV testing in marriage applicants). It can also put more weight on false negatives (e.g., HIV testing in blood donors).
- **Measures observer agreement (kappa).** Interobserver variability can be quantified.
 - A κ of 0.4–0.6 is moderate agreement and 0.6–0.8 is substantial agreement.
 - Chest radiograph infiltrate has only fair to moderate agreement (κ 0.38–0.58).
 - The abdominogugular test has κ **0.92** (almost perfect).
- **Supports multivariable prediction models.** These assign a relative weight to each independent predictor, which is more accurate than reasoning in the head or with Bayes' rule alone.
 - Examples are the ACC/AHA statin risk calculator and the CHA₂DS₂-VASc calculator.
- **Demands independent validation.** A model must be validated in a population separate from the one used to build it. An unvalidated model deserves the scepticism due to an untested new drug.
 - The Wells criteria for pulmonary embolism are a validated example.

- **Exposes hidden assumptions.** Sensitivity and specificity are often assumed to be prevalence-independent, which is often incorrect.
 - Treadmill sensitivity is ~30% in one-vessel CAD but approaches 80% in severe three-vessel CAD.
- **Tests new digital tools.** AI and large language models need independent validation before use in clinical care.

Figure 4-1 — Harrison's 22e, pr.24. **FIGURE 4-1** Each receiver operating characteristic (ROC) curve illustrates a trade-off that occurs between improved test sensitivity (accurate detection of patients with disease) and improved test specificity (accurate detection of patients without disease), as the test value defining when the test turns from "negative" to "positive" is varied. A 45° line would indicate a test with no predictive value (sensitivity = specificity).

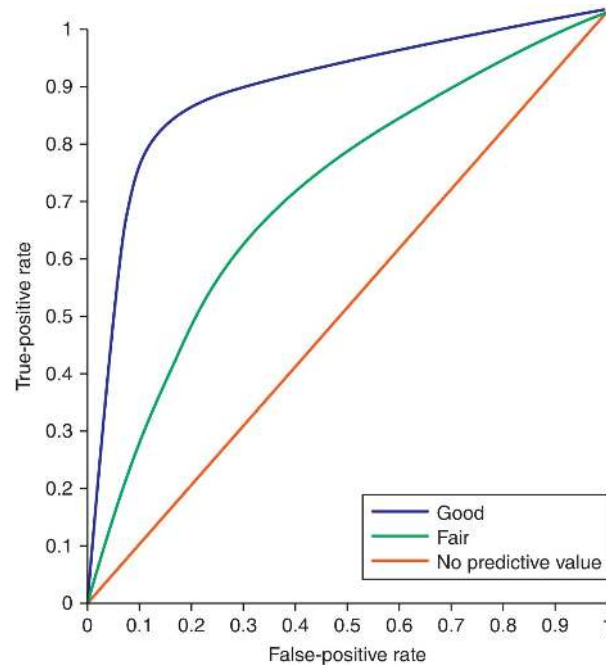


Table 1: Measures of diagnostic test accuracy

Measure	Formula	Meaning
Sensitivity (true-positive rate)	$TP/(TP + FN)$	Detects patients with disease
Specificity (true-negative rate)	$TN/(TN + FP)$	Detects patients without disease
False-positive rate	$1 - \text{specificity}$	Positives among the disease-free
LR positive	$\text{sensitivity}/(1 - \text{specificity})$	How much a positive result raises probability
LR negative	$(1 - \text{sensitivity})/\text{specificity}$	How much a negative result lowers probability

Table 4-1 — Harrison's 22e, pr.24. **TABLE 4-1** Measures of Diagnostic Test Accuracy

TEST RESULT	DISEASE STATUS	
	PRESENT	ABSENT
Positive	True positives (TP)	False positives (FP)
Negative	False negatives (FN)	True negatives (TN)
Test Characteristics in Patients with Disease		
True-positive rate (sensitivity) = $TP/(TP + FN)$		
False-negative rate = $FN/(TP + FN) = 1 - \text{true-positive rate}$		
Test Characteristics in Patients without Disease		
True-negative rate (specificity) = $TN/(TN + FP)$		
False-positive rate = $FP/(TN + FP) = 1 - \text{true-negative rate}$		

How Bayes' rule helps in diagnostic probability

Principle

- **Pretest probability** is the estimated likelihood of the diagnosis before testing.
 - It comes from the prevalence in the population, or from the clinical context (age, sex, type of chest pain).
- The **posttest probability** is the recalibrated probability that accounts for both pretest probability and test result.
- Posttest probability is also called the predictive value of the test. The more descriptive term "posttest probability following a positive or negative test" is preferred.
- Predictive values are calculated probabilities. They are not intrinsic measures of test accuracy.
- Predictive values taken from the study sample are misleading unless the test is applied to populations with exactly the same prevalence.

Formula (positive test)

- Posttest probability = $(\text{pretest} \times \text{sensitivity}) / [(\text{pretest} \times \text{sensitivity}) + (1 - \text{pretest}) \times \text{false-positive rate}]$.

WORKED EXAMPLE

Bayes' rule for a positive test

1. Sensitivity = 0.90 and specificity = 0.90, so the false-positive rate is 0.10.
2. Pretest probability 0.50: $(0.50)(0.90) / [(0.50)(0.90) + (0.50)(0.10)] = \mathbf{0.90}$. This is the textbook example of a 64-year-old woman with atypical chest pain.
3. Pretest probability 0.10: $(0.10)(0.90) / [(0.10)(0.90) + (0.90)(0.10)] = 0.09/0.18 = \mathbf{0.50}$. This agrees with the textbook's 10% pretest patient whose probability rises to 50% after a positive SPECT.
4. LR positive = $0.90/(1 - 0.90) = \mathbf{9}$. LR negative = $(1 - 0.9)/0.9 = \mathbf{0.11}$.

Likelihood-ratio (nomogram) form

- The LR summarises the impact of a test result. It is the probability of that result in diseased patients divided by its probability in non-diseased patients.
- The LR for a positive test is the true-positive rate divided by the false-positive rate. The LR for a negative test is the false-negative rate divided by the true-negative rate.
- Most tests have an LR positive between 1.5 and 20.
- An LR positive >10 usually implies high specificity, which helps rule in disease (SpPin).
- An LR negative <0.10 usually implies high sensitivity, which helps rule out disease (SnNout).
- Excellent sensitivity with poor specificity gives a weak LR. For example, 90% sensitivity with 55% specificity gives an LR positive of 2.0.
- LRs >1 raise probability and LRs <1 lower it.
- Bedside rule of thumb (McGee):
 - LRs of 2, 5 and 10 raise probability by about 15, 30 and 45%.
 - LRs of 0.5, 0.2 and 0.1 lower it by about 15, 30 and 45%.
 - These estimates are accurate to within 5–10% of the calculated value.

Figure 4-2 — Harrison's 22e, pr.25. **FIGURE 4-2** Nomogram version of Bayes' theorem used to predict the posttest probability of disease (right-hand scale) using the pretest probability of disease (left-hand scale) and the likelihood ratio for a positive or a negative test (middle scale). See text for information on calculation of likelihood ratios. To use, place a straightedge connecting the pretest probability and the likelihood ratio and read off the

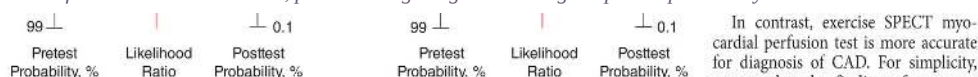


Table 2: Bayes' rule in coronary artery disease

Test	LR+	Pretest 10% → posttest	Pretest 80% → posttest
Exercise treadmill (sens ~60%, spec ~75%)	2.4	~30%	~95%
Exercise SPECT (sens and spec 90%)	9.0	50%	97%

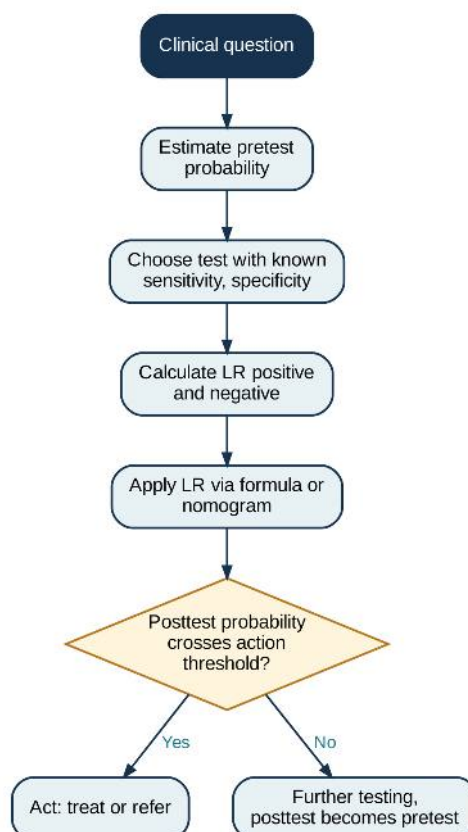
Clinical lessons from Bayes' rule

- **The biggest change in probability occurs when the clinician is most uncertain.** This is a pretest probability of 30–70%.
 - Example: at a pretest of ~50%, a positive treadmill raises the probability to 80% and a positive SPECT to 90%.
- **A more accurate test may not change management.** At a pretest of 10%, SPECT only moves the clinician from "fairly certain no CAD" to 50:50.
- **At low pretest probability, even an accurate test cannot rule in disease.** An LR of 10 with a pretest of 20% does not reach 80%.
- **Screening needs high specificity.** Pretest probabilities are low because patients are asymptomatic.
 - In first-time female blood donors, specificity was 99.995% and prevalence 0.01%. A positive test raised the likelihood of HIV only to 67%.
- **At high pretest probability, a negative test may not exclude disease** if the test is not sufficiently sensitive.
- **Pretest probabilities can be taken from tables for common settings:**
 - cough and fever → pneumonia, median 22% (range 15–35%)
 - pleuritic chest pain, dyspnoea or haemoptysis → pulmonary embolism, median 25%
- **Physical signs also carry LR.** Examples:
 - Clubbing for hepatopulmonary syndrome in chronic liver disease has an LR of 4.3 when present.
 - A positive abdominojugular test for raised left heart filling pressure has an LR of 8.0 when present and 0.3 when absent.
 - Signs marked "NS" have an LR no different from 1.0 and are useless for that diagnosis.

Limitations of Bayes' rule

- Few tests give only "positive" or "negative" results. Multidimensional results (e.g., extent of ST depression, exercise duration) make the calculation more complex.
- Sequential tests can use the previous posttest probability as the next pretest probability. This assumes **conditional independence**, which is often untrue.
- Sensitivity varies with disease severity in the local population. Sensitivity is likely higher in hospitalised patients and specificity higher in outpatients.
- Multivariable models (e.g., logistic regression) address these problems better, but usually need a calculator or computer.

Flowchart 1: Applying Bayes' rule at the bedside



PEARLS

- Sensitivity = $TP/(TP + FN)$ and specificity = $TN/(TN + FP)$. **SnNout** and **SpPin** are the rule-out and rule-in mnemonics.
- The ROC area runs from **0.5** (useless) to **1.0** (perfect). A stricter cut point lowers sensitivity and raises specificity.
- Posttest probability needs three inputs: **pretest probability, sensitivity, specificity**.
- $LR+ = \text{sensitivity}/(1 - \text{specificity})$. $LR- = (1 - \text{sensitivity})/\text{specificity}$. $LR+ > 10$ helps rule in disease and $LR- < 0.10$ helps rule out disease.
- McGee's rule of thumb: LR 2, 5, 10 add about 15, 30, 45%; LR 0.5, 0.2, 0.1 subtract about 15, 30, 45%.
- Tests change probability most when the pretest probability is **30–70%**.
- In screening, low prevalence makes specificity paramount. Even a 99.995%-specific HIV test gave only a 67% posttest probability at 0.01% prevalence.
- Sequential use of Bayes' rule assumes conditional independence, which is often untrue.
- Prediction models must be independently validated before use. The Wells score for pulmonary embolism is a validated example (>6.0 high, $2.0\text{--}6.0$ intermediate, <2.0 low).

2. Tools for assessing quality of health care

ASKED 1* • Intermediate answer

Asked in: May 2024 P-IV Q10(b) (5 marks)

Q: Discuss the tools for assessment of quality of healthcare. [5]

SOURCE Harrison's 22e — Ch 7 The Safety and Quality of Health Care, §Prevention Strategies to National State of Quality Measurement — pp. 43–45
Harrison's 22e — Ch 11 Racial and Ethnic Disparities in Health Care, §Root Causes of Disparities — p. 62

Definition

- Quality of care is judged by measurement, and Harrison's describes selection and measurement of quality as parts of a complex process.
- Assessment tools fall into four groups: the Donabedian framework, improvement cycles with statistical tools, quality metrics and reporting systems, and national datasets and benchmarking.
- Safety measurement is a related but separate area. It is covered briefly below because safety is part of quality.

Donabedian framework (structure–process–outcome)

- Donabedian classified quality measurement into **structure, process and outcome**.
- **Structure** asks whether a characteristic is present in a setting. Examples are a hospital with a catheterisation laboratory, or a clinic using an electronic health record (EHR).
- **Process** is the way care is delivered. Examples are a Pap smear done at the recommended interval, or aspirin given in suspected myocardial infarction.
- **Outcome** is what happens to the patient. An example is the mortality rate in myocardial infarction.
- Good structure and process do not always give a good outcome. A patient may reach a cath-lab centre, receive aspirin and still die of the infarction.
- Process measures are easier to improve than outcome measures. In diabetes care, improving the HbA1c level was harder than improving whether HbA1c was measured.
- The link between process measures and outcomes varies by condition. It is strong for Pap smears and cervical cancer outcomes, but weaker for many other conditions.

Table 1: Donabedian domains with examples

Domain	Question asked	Example
Structure	Is the resource or characteristic present?	Cath lab; EHR in clinic
Process	Was recommended care delivered?	Aspirin in suspected MI; Pap smear interval
Outcome	What happened to the patient?	MI mortality; HbA1c level

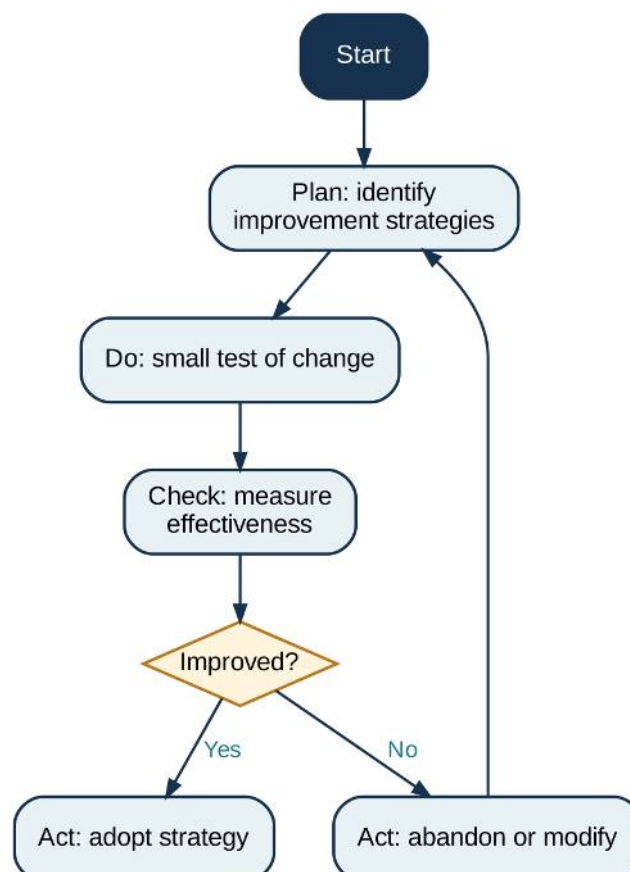
Continuous quality improvement tools

- Continuous quality improvement means organisations evaluate their care on an ongoing basis and keep making small changes to their processes.
- The **Plan-Do-Check-Act (PDCA) cycle** is one of the most important tools.
 - Plan:** identify potential improvement strategies.
 - Do:** try the strategies in small "tests of change".
 - Check:** measure whether the strategies made a difference.
 - Act:** adopt or abandon the strategies based on the results.
- PDCA suits "rapid cycle" improvement of a process. An example is the time from diagnosis of pneumonia to the first antibiotic dose.
- Control charts** are statistical tools used alongside PDCA to show whether progress is being made.

Figure 7-2 — Harrison's 22e, pr.44. **FIGURE 7-2** Plan-Do-Check-Act cycle. This approach can be used to improve a specific process rapidly. First, planning is undertaken, and several potential improvement strategies are identified. Next, these strategies are evaluated in small "tests of change." "Checking" entails measuring whether the strategies have appeared to make a difference, and "acting" refers to acting on the results.



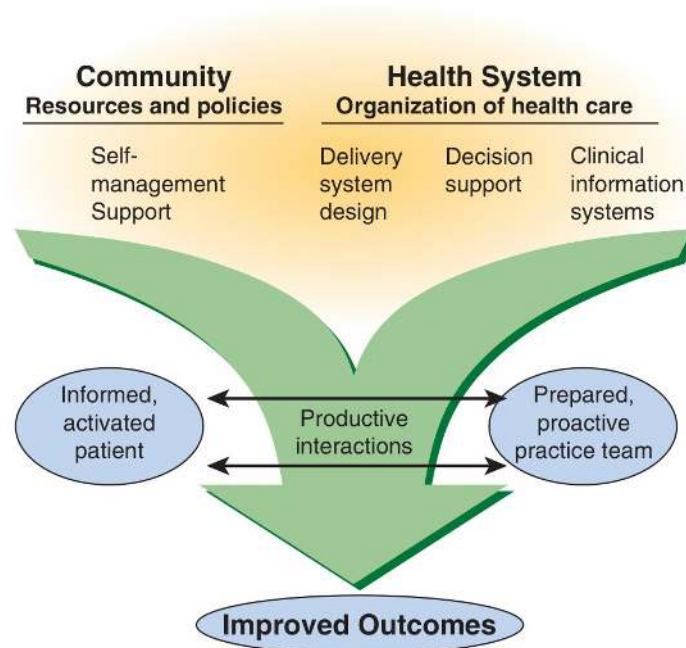
Flowchart 1: PDCA cycle for assessing and improving quality



Systems-level tools and quality-improvement strategies

- Quality theory holds that raising the performance of all providers improves overall quality more than identifying and punishing a few poor performers. Systems change therefore matters.
- **Reminders** about the actions needed at a visit improve delivery of preventive services.
- **Bundles** are groups of measures implemented together with high fidelity. The ventilator-associated pneumonia (VAP) bundle has five measures, such as head-of-bed elevation.
- **Checklists** have sharply reduced catheter-associated bloodstream infection and VAP in ICUs.
- **SCAMPs** (Standardized Clinical Assessment and Management Plans) are clinician-developed guidelines. They identify key steps in workflow and decisions to improve process outcomes.
- The **Chronic Care Model** is used to improve chronic disease care.
 - It combines self-management support, delivery system design, decision support and clinical information systems.
 - It is delivered by a practice team, not by a physician alone.
 - Team changes and case managers were the most effective strategies for lowering HbA1c.

Figure 7-3 — Harrison's 22e, pr.44. **FIGURE 7-3** The Chronic Care Model, which focuses on improving care for chronic diseases, suggests that (1) delivery of high-quality care requires a range of strategies that must closely involve and engage the patient and (2) team care is essential. (From EH Wagner et al: *Eff Clin Pract* 1:2, 1998.)



- Individual-level strategies are rationing, education, feedback, incentives and penalties.
 - Education works in the short term, but its effect decays quickly.
 - Feedback is most effective when it is individualised and given close in time to the event.
 - Penalties cause resentment and are rarely used.

Quality metrics, data sources and reporting

- The **Hospital Quality Initiative** measures 20 indicators across myocardial infarction, heart failure, pneumonia and surgical infection prevention.
- Its data are publicly released on the Hospital Compare website.
- Medicare is moving to **electronic clinical quality measures (eCQMs)**, which are extracted from EHRs rather than claims. These still need validation.
- Claims-based metrics contain many inaccuracies, and some metrics can be "gamed".
- **Public reporting** has had little direct use by patients, but it has influenced provider and organisation behaviour.
- **Pay-for-performance** pays more for higher-quality care.
 - Its key issues are effectiveness, the incentive level needed, and perverse consequences.

- Perverse consequences include transferring the sickest patients away and neglecting unmeasured aspects of care.
- Benchmarking datasets also assess quality.
 - The RAND 2006 study found US patients received **55%** of recommended care.
 - Dartmouth Atlas data show no positive correlation between utilisation and quality across regions. Higher-volume providers have better outcomes.
- Disparities reports track measures across groups. The 2022 US National Healthcare Quality and Disparities Report follows more than 400 process, outcome and access measures.

Measuring safety, a component of quality

- Spontaneous reporting is the commonest tool, but it is insensitive and captures only about **1 in 20** adverse drug events.
- Other tools are chart review, computerised ADE monitors, electronic-record trigger searches and claims data.
- Using several approaches together finds more events than any single one.
- Claims data work better for surgical care than for medical care.
- Reporting by providers remains a duty, because reported events serve as lessons for improvement.

Table 2: Quality-assessment tools compared

Tool	Level	Main strength	Main limitation
Donabedian triad	Conceptual framework	Covers structure, process and outcome	Good structure and process do not guarantee outcome
PDCA with control charts	Process	Rapid, small-scale testing	Applies to one process at a time
Bundles and checklists	Unit	High-fidelity delivery	Needs full compliance
Claims and eCQMs	System	Large-scale data	Inaccuracies; eCQMs need validation
Spontaneous reporting	Safety	Easy to run	Very low sensitivity

PEARLS

- Donabedian's triad is **structure, process, outcome**. Good structure and process do not guarantee good outcome.
- PDCA is the core rapid-cycle tool, used with control charts.
- It is easier to improve process measures than outcome measures.
- Raising the performance of all providers beats punishing a few outliers.
- The VAP bundle has five measures. Checklists cut central-line infection and VAP.
- The Chronic Care Model needs a team, not a physician alone.
- Spontaneous reporting captures only about 1 in 20 ADEs.
- The RAND study found 55% of recommended care delivered.
- Pay-for-performance risks cherry-picking patients and neglect of unmeasured care.

3. Communication skills in health-care workers

ASKED 1* • Intermediate answer

Asked in: Jun 2022 P-IV Q9(b) (5 marks)

Q: Write about communication skills in health care workers. [5]

SOURCE Harrison's 22e — Ch 11 Racial and Ethnic Disparities in Health Care, §Provider-Level Factors, Patient-Level Factors, Patient Interventions — pp. 66–69
Harrison's 22e — Ch 12 Ethical Issues in Clinical Medicine, §Approaches to Ethical Problems — p. 70

Definition

- Communication in health care is the **two-way exchange of information, understanding and emotion** between health-care worker (HCW) and patient, family and team.
- Effective communication is linked to **patient satisfaction, regimen adherence and better health outcomes**.

- Patient-centredness covers compassion, empathy and responsiveness to the patient's needs, values and expressed preferences.

Why it matters

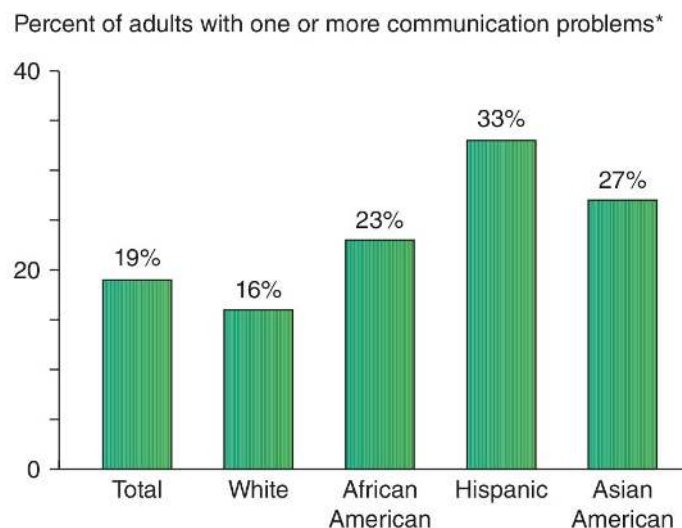
- Poor communication produces patient dissatisfaction, poor adherence, poorer outcomes and disparities in care.
- Patients and HCWs differ in how they recognise symptoms, in their thresholds for seeking care, and in their understanding of management. They also differ in their expectations of care and in adherence.
- Language barriers lead to misunderstood diagnosis and follow-up, inappropriate medication use, and lack of informed consent. They also lead to more adverse events.
- Physicians with access to trained interpreters report significantly better communication quality than those using other methods.
- In a survey of 6722 adults, **19%** reported at least one communication problem: trouble understanding the doctor, not feeling listened to, or being afraid to ask questions.

Figure 11-8 — Harrison's 22e, pr.66. **FIGURE 11-8** The link between effective communication and patient satisfaction, adherence, and health outcomes. (From the Institute of Medicine. 2003. *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*. <https://doi.org/10.17226/12875>. Adapted and reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.)

How do we link communication to outcomes?



Figure 11-9 — Harrison's 22e, pr.66. **FIGURE 11-9** Communication difficulties with physicians, by race/ethnicity. The reference population consisted of 6722 Americans ≥18 years of age who had made a medical visit in the previous 2 years and were asked whether they had had trouble understanding their doctors, whether they felt that the doctors had not listened, and whether they had had medical questions they were afraid to ask. (Reproduced with permission)



Base: Adults with health care visit in past two years

*Problems include understanding doctor, feeling doctor listened, had questions but did not ask.

Components of effective communication

Respecting the patient

- Respect means understanding the patient's goals and giving information. It also means communicating effectively, obtaining informed and voluntary consent, respecting informed refusal, and protecting confidentiality.
- Confidentiality, professional boundaries and therapeutic relationships must be considered in all spoken and written communication.

Giving information and breaking bad news

- Give accurate information on diagnosis, expected course, prognosis, options and uncertainties.
- Do not withhold a serious diagnosis or blur it with ambiguous terms to avoid causing anxiety. Honest information promotes **autonomy and trust**.
- When sharing bad news:
 - Adjust the **pace of disclosure**.
 - Offer empathy and hope, and give emotional support.
 - Call on other resources such as spiritual care or social work.
- Some patients choose not to receive information, or ask surrogates to decide. This is common in some cultures, so ask about preferences.

Shared decision-making and informed consent

- Inform and educate the patient, elicit and answer questions, and check understanding.
- Then make a recommendation and help the patient to deliberate.
- Avoid jargon, needlessly complicated explanations, and too much information at once.
- Decision aids improve the accuracy of risk–benefit perception and help clarify values.
- Informed consent is more than a signature. It requires honest, understandable disclosure that promotes understanding and choice.
- In an emergency, treatment may proceed without consent if the patient cannot consent and delay would be harmful.

Cross-cultural skills

- Cultural competence has moved from learning "dos and don'ts" about groups, which risks stereotyping, to patient-centred skills.
- Skills include:
 - Using interpreter services.
 - Eliciting the patient's understanding of the condition.
 - Assessing decision-making preferences and the family's role.
 - Asking about views on biomedicine versus complementary and alternative medicine.
 - Recognising sexual and gender issues, and building trust.
- Treat the patient as teacher and adjust your practice style to their needs.

Barriers to communication

Table 1: Barriers to HCW–patient communication

Level	Barrier	Effect
Language	Limited proficiency, no trained interpreter	Misunderstanding, errors, invalid consent
Clinician	Stereotyping, implicit bias	Less patient-centred communication
Clinician	Stress, multitasking, time pressure	Stereotypes activated most
Patient	Mistrust	Poor adherence, doctor-shopping, self-medication
Style	Jargon, information overload	Patient overwhelmed

- Stereotyping is a subconscious simplification of decisions using social categories. It differs from **prejudice** (conscious prejudgment) and **discrimination** (conscious, intentional disparate treatment).
- In one survey of about 16,000 physicians, **42%** admitted that bias affected their decisions.
- Clinical uncertainty arises when symptom expression is hard to read. It can alter decisions even without prejudice.

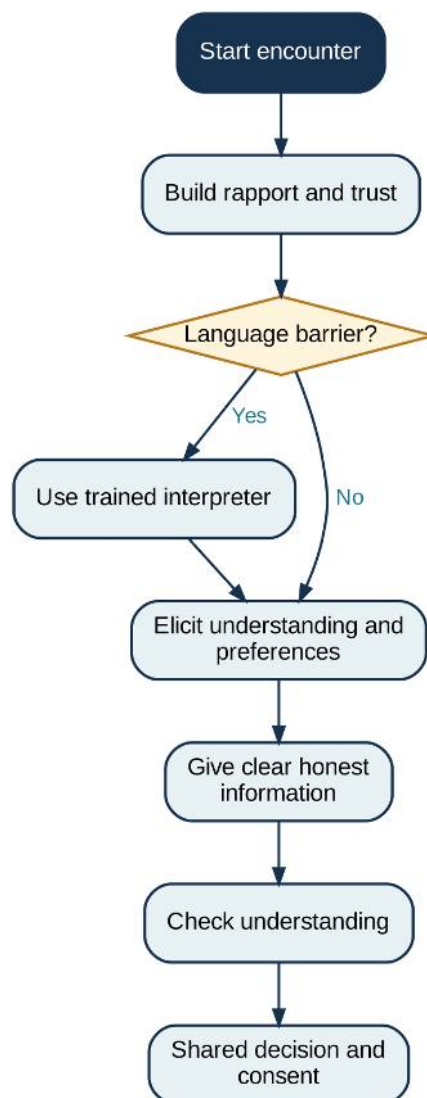
Building trust

- Trust facilitates open communication and correlates directly with adherence and satisfaction.
- Strategies:
 - Be aware that mistrust exists.
 - Reassure patients that they come first and that the caregiver is their advocate.
 - Show honesty, openness, compassion and respect.
 - Use shared, participatory decision-making and try to understand the patient's background.

Avoiding stereotyping

- Work in diverse teams in which every member has equal power and a common goal.
- Monitor your own behaviour, and check that you offer the same things in the same ways to all patients.

Flowchart 1: Stepwise approach to a clinical communication encounter



Team and system level

- Teaching on how race, ethnicity and culture affect communication and decisions is mandated in medical education.
- Patients should be educated to navigate the system, and interventions should increase their participation in decisions.
- An ethics consultation service or committee can help improve communication and resolve conflicting emotions.

PEARLS

- Good communication improves **satisfaction, adherence and outcomes**.
- Use a **trained interpreter** rather than ad hoc methods.
- Stereotyping is subconscious; prejudice and discrimination are conscious.
- Stereotypes are strongest under **stress, multitasking and time pressure**.
- Break bad news by adjusting pace, offering empathy and hope, and involving support services.
- Informed consent is a process of understandable disclosure, not just a signature.
- Avoid jargon and information overload.
- Cultural competence today means patient-centred skills, not group "dos and don'ts".
- Trust is built through honesty, openness, compassion, respect and shared decisions.

4. Ethical principles and conflicts of interest in the medical profession

ASKED 1* · Long answer

Asked in: May 2024 P-III Q3(a) (5 marks) · May 2024 P-III Q3(b) (5 marks)

Q: What are ethical principles? [5]

Q: Discuss the various conflicts of interest in medical profession. [5]

SOURCE Harrison's 22e — Ch 1 The Practice of Medicine, §Electronic Medical Records; The Patient–Physician Relationship — p. 5
Harrison's 22e — Ch 12 Ethical Issues in Clinical Medicine, §Approaches to Ethical Problems; Ethical Principles; Acting Justly — pp. 70–71

Definition and why it matters

- **Ethics** here means the principles that tell a physician the right thing to do in a clinical situation. They are "general guidelines to help physicians determine the right thing to do".
- Physicians make ethical judgments about clinical situations **every day** and should prepare for lifelong learning about ethical issues.
- The chapter names several causes of ethical dilemmas:
 - intensity of care at the end of life
 - how to distribute time between critically ill patients
 - responsibility for patients with limited access to care
 - artificial intelligence, which raises concerns about confidentiality, the doctor–patient relationship and accountability
 - health disparities and the growth of for-profit enterprises
- Traditional codes and principles give guidance, but they must be **interpreted and applied** to each situation.
- Ethical dilemmas can be perplexing and emotionally draining, and can sometimes lead to **moral distress**.
- **Conflict of interest** arises when a physician's duty to the patient competes with another interest. That interest may be the physician's own, an institution's, a third party's or a competing patient's.

Approaches to ethical problems

- Four sources of guidance are used:
 - ethical principles
 - virtue ethics
 - professional oaths
 - personal values
- These sources may seem to **conflict**, and different individuals in a diverse society turn to different sources.
- General moral precepts need interpretation for each clinical situation.

Ethical principles (Part a)

Table 1: Core ethical principles and their clinical meaning

Principle	Meaning	Clinical application
Respect for patients (autonomy)	Treat patients with respect and honour their informed choices	Informed consent, informed refusal, confidentiality, capacity assessment
Beneficence	Act for the patient's benefit; a fiduciary duty	Compassion, sound recommendations, patient's interests above self-interest
Non-maleficence	"First do no harm"	Maximise benefit, minimise harm; avoid ineffective interventions
Justice	Fairness; similar treatment of similar people	No discrimination; fair allocation of resources and the physician's own time

1. Respect for patients (autonomy)

- Respect means:
 - understanding the patient's goals
 - providing information
 - communicating effectively
 - obtaining **informed and voluntary consent**
 - respecting informed refusals
 - protecting confidentiality
- Individuals differ in how they value health and weigh benefits against risks, so physicians should respect patients' values and informed choices.
- Respect is especially important when patients have experienced or fear disrespect and discrimination.
- Autonomy and the physician's duty to act in the patient's best interest are the two fundamental principles reflected in informed consent.
- Competent, informed patients may refuse recommended interventions and choose among reasonable alternatives.
- Respect for patients **does not entitle them to demand any treatment**. Physicians are not obliged to give interventions that:
 - have no physiological rationale
 - have already failed
 - are contrary to evidence-based recommendations or good clinical judgment

2. Beneficence (acting in the patient's best interests)

- Beneficence requires the physician to act for the patient's benefit.
- Patients usually lack medical expertise and are made vulnerable by illness, so they trust the physician to be compassionate and give sound advice.
- The physician has a **fiduciary duty**. The patient's best interests should prevail over the physician's self-interest and over the interests of third parties such as hospitals or insurers.
- Care is delivered through interdisciplinary teams and referral:
 - team members should collaborate and respect one another's contributions
 - they should communicate and plan regularly to avoid diffusion of responsibility and ensure accountability
- Beneficence may need practical steps such as prescribing **affordable** medicines.

3. Non-maleficence ("first do no harm")

- This principle obliges the physician to prevent unnecessary harm:
 - recommend interventions that maximise benefit and minimise harm
 - never give known ineffective interventions
 - never act without due care
- The precept alone gives limited guidance, because many beneficial interventions also carry serious risks.

- Standardised protocols and checklists reduce infection, wrong-site surgery and falls, which is non-maleficence in practice.

4. Justice

- Justice means fairness: people receive what they are owed.
- Similar people are treated similarly in ethically relevant ways, which avoids arbitrary, biased or unfair decisions.
- Justice forbids discrimination based on race, religion, gender, sexual orientation, disability, age or other personal characteristics.
- It guides the allocation of important resources, including the physician's own time.
- **Distributive justice** requires fair distribution of resources.
- Equity means no variation in quality of care due to personal characteristics such as race or ethnicity.

Practical applications of the principles

Informed consent

- Consent is the practical expression of respect for the patient.
- The physician must:
 - communicate clearly
 - discuss the alternatives
 - explain risks, benefits and likely consequences
 - ensure the patient understands
 - encourage questions
 - repeat explanations where needed
- Informed consent is more than obtaining signatures. It involves disclosure of honest, understandable information that promotes understanding and choice.
- **Emergency exception:** treatment may be given without consent if the patient cannot consent and delay while contacting surrogates would jeopardise life or health.
 - Patients are presumed to want emergency care unless they have indicated otherwise, for example through a portable order for life-sustaining treatment (POLST).

Shared decision-making and truth-telling

- Shared decision-making involves informing patients, eliciting and answering questions, checking understanding, making recommendations and helping patients deliberate.
- Jargon, over-complicated explanations or too much information at once can overwhelm patients.
- Decision aids improve the accuracy of risk–benefit perception.
- Physicians may be tempted to withhold or blur a serious diagnosis, but honest information promotes autonomy and trust.
- When breaking bad news:
 - adjust the pace
 - offer empathy and hope
 - provide emotional support
 - involve spiritual care or social work
- Some patients may choose not to receive information, or ask surrogates to decide.

Capacity and surrogates

- A patient with capacity can:
 - express choices
 - appreciate the situation, the nature, risks and benefits of care, and the consequences of each alternative
 - make choices consistent with their values, not driven by delusion or misinformation
- Physicians usually judge capacity, using validated tools, psychiatry or ethics consultation, and clinical judgment. Courts determine legal incompetence.

- A patient who refuses treatment must **not be assumed to lack capacity**, but the refusal should be probed.
- If impairment is fluctuating or reversible, postpone the decision and revisit it.
- Surrogate order:
 - a proxy named in an advance directive or POLST
 - family members
 - a fair institutional or legal process for unrepresented patients
- Surrogates should be guided by the patient's values, goals and prior preferences.

Confidentiality

- Confidentiality is essential to autonomy and privacy, and it encourages candid discussion.
- It may be overridden only when all of the following hold:
 - the risk is serious and probable
 - no less restrictive measure can avert it
 - the adverse effects of breaching are minimised and acceptable to society
- Laws require reporting of tuberculosis, sexually transmitted infections, elder or child abuse and domestic violence.

Care of the dying

- Transparency delivered appropriately is essential in terminal illness.
- The goal shifts from **cure to care**, guided by *primum succurrere*, "first, to help".
- Pain control, preserved dignity and avoidance of isolation are part of ethical care.

Conflicts of interest in the medical profession (Part b)

- A conflict of interest exists when a physician's duty to the patient competes with another interest.
- Harrison's principle is that the patient's best interests prevail over the physician's self-interest and over third parties such as hospitals or insurers.

Table 2: Types of conflict of interest and how to manage them

Type	Example from the text	Management
Physician's self-interest vs patient	Self-interest or institutional/insurer interest competing with the patient's welfare	Fiduciary duty; patient's interest prevails
Consent-seeker's conflict	Physician seeking consent has a real or apparent conflict of interest	Ensure none exists, or disclose and avoid
Commercial / for-profit pressures	Growth of for-profit enterprises; escalating drug prices and out-of-pocket costs	Prescribe affordable, acceptable drugs; follow up on unfilled prescriptions; use pharmacists and social workers; advocate for non-formulary drugs when justified
Institutional / workplace	Staffing inadequacy, unfair wages, poor equipment, work-hour limits, corporate culture, violence	Work with institutional leaders so policies support patient-focused care
Documentation and billing	EMR data entry to meet billing requirements; "cut and paste" shortcuts raise error risk	Preserve face-to-face contact; avoid shortcuts; remember IT is only a tool
Guidelines vs the individual patient	A guideline may not serve a patient when another plan would give substantially greater benefit	Know the guidelines, recognise justified exceptions, advocate for them
Competing patients / resources	Distributing time between critically ill patients; scarce resources in a public health crisis	Justice; fair, transparent allocation under public policy
Conflict among duties	Confidentiality vs protecting third parties; autonomy vs best interests	Override only under strict criteria; persuade first, then use institutional resources

Conflicts within the patient–physician relationship

- **Autonomy vs best interests:**
 - Refusals or requests may thwart the patient's own goals or cause serious harm.

- Example: accepting a young asthmatic's refusal of ventilation for readily reversible respiratory failure is "morally constricted".
- Elicit expectations and concerns, correct misunderstandings and try to persuade.
- If disagreement persists, call on institutional resources, but the patient's **informed choices and own view of best interests prevail**.
- **Surrogate decisions vs the patient's current best interests:** earlier preferences may be overridden if an intervention gives significant benefit, prior statements do not fit, or the surrogate was given leeway.
- **Disclosure vs fear of causing distress:** the temptation to withhold diagnosis conflicts with honesty.
 - Family members may also try to shield the patient from the diagnosis.

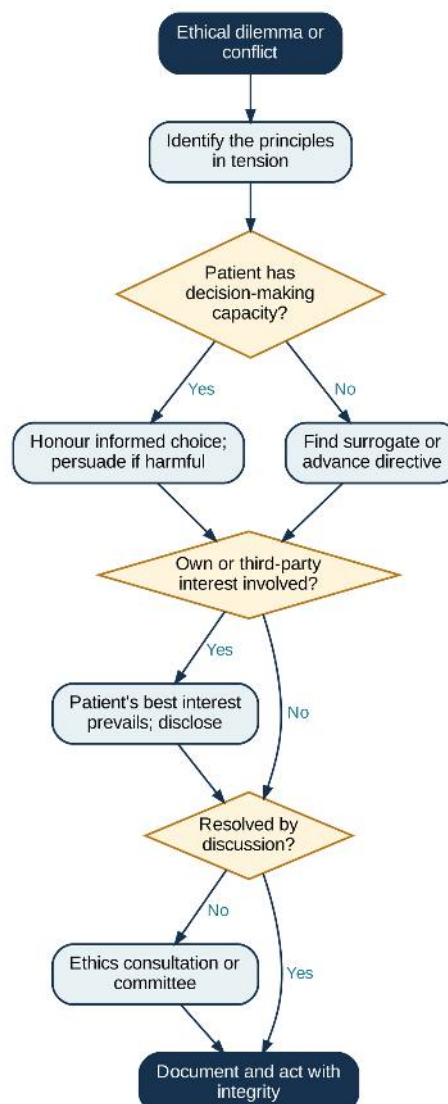
Conflicts arising from technology

- AI promises coordinated, efficient care but raises confidentiality, doctor–patient relationship and accountability concerns.
- EMRs improve access and quality, but they can create distance between physician and patient and cause dissatisfaction and lower physician well-being.

Resolving conflicts: a practical approach

- Articulate your concerns and reasoning.
- Listen to and respect others involved in the patient's care.
- Use the interdisciplinary team and, if needed, ethics consultants or the hospital ethics committee.
- Be prepared to reassess your own basic convictions, tolerate uncertainty and act with integrity.

Flowchart 1: Approach to an ethical dilemma or conflict of interest



Professionalism: the patient–physician relationship

- The ideal relationship rests on thorough knowledge of the patient, **mutual trust** and the ability to communicate.
- Empathy and compassion are the essential features of a caring physician.
- Patients are not "cases" or "diseases". "Patients do not fail treatments; treatments fail to benefit patients".
- The physician must consider the patient's familial, social and cultural background.

PEARLS

- The four classical principles are **respect for patients (autonomy), beneficence, non-maleficence ("first do no harm") and justice**.
- Beneficence carries a **fiduciary duty**. The patient's interests outrank the physician's self-interest and those of hospitals or insurers.
- Informed consent is a process of honest, understandable disclosure, not just a signature.
- In an emergency, treat without consent if the patient cannot consent and delay would jeopardise life or health.
- Refusal of treatment does not by itself mean lack of capacity, but it should be probed.
- Confidentiality may be breached only if the risk is serious and probable, no less restrictive measure exists, and the harm of breaching is minimised.
- A physician seeking consent must have no real or apparent conflict of interest.
- Respecting autonomy does not oblige a physician to give futile or evidence-contrary treatment.
- Resolve dilemmas through communication, the team and ethics consultation or committee.
- In terminal illness the goal shifts from cure to care.

5. Informed consent

ASKED 1* · Intermediate answer

Asked in: Dec 2022 P-IV Q6(a) (5 marks)

Q: *Informed consent*. [5]

SOURCE Harrison's 22e — Ch 12 Ethical Issues in Clinical Medicine, §Approaches to Ethical Problems; Acting Justly (incl. Beneficence) — pp. 70–71

Definition

- **Informed consent** is a process, not a form: honest, understandable disclosure that promotes the patient's understanding and choice.
- It is more than obtaining signatures on consent forms.
- It rests on respect for the patient's autonomy: physicians should respect patients' values and informed choices.
- Competent, informed patients may refuse recommended interventions and choose among reasonable alternatives.

Why it matters

- It promotes autonomy and trust; honest information about clinical circumstances supports both.
- It is part of respecting patients, together with understanding their goals, effective communication, respecting informed refusals and protecting confidentiality.
- Withholding or blurring a serious diagnosis for fear of anxiety or depression is ethically discouraged.
- Patients differ in how they value health and weigh benefit against risk, so consent must be individualised.

Essential elements

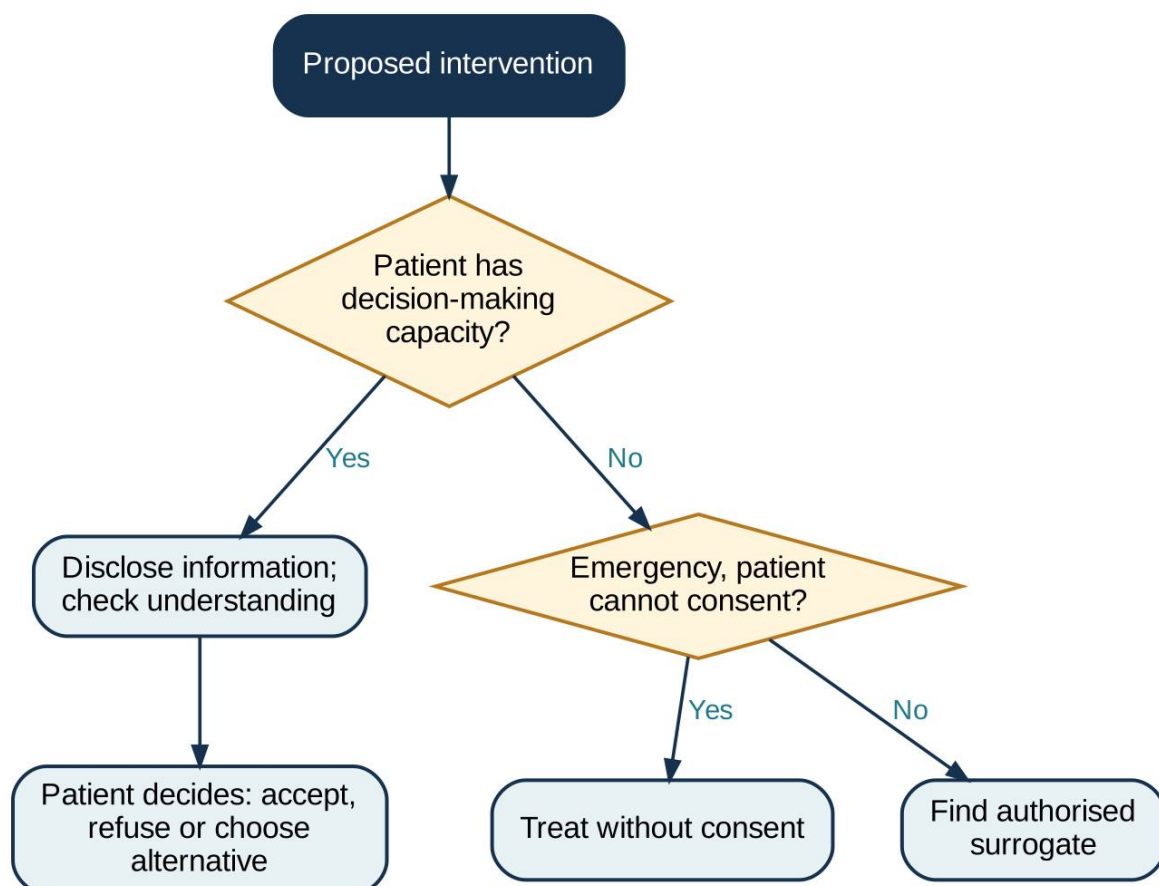
Table 1: Elements of valid informed consent

Element	Content	Note
Capacity	Can express a choice and appreciate their situation, the nature, risks and benefits of the proposed care, and the consequences of each alternative	Choice must fit the patient's values and not result from delusions, hallucinations or misinformation
Disclosure	Diagnosis, expected course, prognosis, treatment options and uncertainties	Relate options to the patient's goals of care
Understanding	Physician elicits and answers questions and checks that key issues are understood	Avoid jargon and information overload
Voluntariness	Choice free of coercion	Voluntary consent is part of respecting patients
Decision	Physician makes a recommendation and helps the patient deliberate	Patient may accept, refuse or choose an alternative

Process: shared decision-making

- Engage in **shared decision-making** whenever appropriate.
- Inform and educate the patient.
- Elicit and answer questions.
- Check understanding of key points.
- Make a recommendation and help the patient to deliberate.
- Decision aids help patients take a more active role, perceive risk and benefit more accurately, and clarify their values and goals.
- When breaking bad news, adjust the pace of disclosure, offer empathy and hope, and give emotional support. Involve spiritual care or social work where needed.
- Some patients choose not to receive information or ask surrogates to decide. This is common with serious diagnoses in some cultures, and it should be respected.

Flowchart 1: Approach to obtaining consent



Exceptions and limits

- **Emergency:** treatment may be given without consent if the patient cannot consent and delay while contacting surrogates would jeopardise life or health.
- Emergency care is presumed to be wanted unless the patient previously indicated otherwise, for example through a portable order for life-sustaining treatment (POLST).
- Respect for patients does not entitle them to demand any treatment they want.
- Physicians need not provide interventions with no physiologic rationale, those that have already failed, or those contrary to evidence-based practice or good clinical judgment.
- Public policy and law govern some decisions, such as allocating scarce resources in public health crises, use of cadaveric organs and requests for physician aid in dying.

Patients lacking capacity

- Decision-making capacity is assessed for the particular decision. Physicians usually determine it and arrange surrogates without involving courts.
- Courts have the legal authority to declare a patient legally incompetent.
- Use validated assessment tools, psychiatry or ethics consultation, and clinical judgment.
- Causes of incapacity include unconsciousness, advanced dementia, delirium and other conditions that impair cognition.
- Refusing treatment or disagreeing with advice does not mean the patient lacks capacity. Probe the decision to exclude misunderstanding.
- If impairment is fluctuating or reversible, postpone the decision if possible and revisit it when capacity returns.
- Surrogate hierarchy:
 - A health care proxy named in an advance directive or POLST, which should be respected.
 - Otherwise family members usually serve as surrogates.
 - For unrepresented patients, follow a fair and careful institutional or legal process.
- Surrogates are guided by the patient's values, goals and previously expressed preferences.
- Current best interests may justify overriding earlier preferences if significant benefit is likely, the earlier statements do not fit the situation, or the patient gave the surrogate leeway.

Refusal and conflict with best interests

- Accepting a refusal that thwarts the patient's own goals, for example a young asthmatic refusing ventilation for readily reversible respiratory failure, is morally constricted.
- Elicit the patient's concerns, correct misunderstandings and try to persuade.
- If disagreement persists, seek institutional help, but the patient's informed choice and view of their own best interests should prevail.

Confidentiality link

- Confidentiality supports autonomy and privacy and encourages candid disclosure.
- It may be overridden when the risk of serious harm is serious and probable, no less restrictive measure works, and the adverse effects are minimised.
- Laws require reporting of tuberculosis, sexually transmitted infections, elder or child abuse and domestic violence.

Practical points for Indian wards

- Document the discussion: what was disclosed, the questions asked and the decision made.
- Obtain consent in a language the patient understands.

PEARLS

- Informed consent is a communication process, and the signed form only records it.
- Five elements: capacity, disclosure, understanding, voluntariness, decision.
- Emergency exception: the patient cannot consent and delay would jeopardise life or health.
- Refusing advice does not mean the patient lacks capacity. Probe for misunderstanding.
- Capacity is decision-specific. If impairment is fluctuating or reversible, defer the decision and revisit it.
- Physicians need not provide futile or non-evidence-based interventions on demand.
- Surrogates follow the patient's values and prior wishes. Best interests may override them in limited circumstances.
- Avoid jargon and information overload. Use decision aids.
- Confidentiality can be breached only for serious, probable harm, with minimal intrusion.

6. Euthanasia and physician-assisted suicide

ASKED 2* • Intermediate answer

Asked in: Dec 2021 P-I Q8(a) (5 marks) • May 2024 P-I Q8(b) (5 marks)

Q: Euthanasia and its various types. [5]

Q: What is Euthanasia and physician assisted suicide? [5]

SOURCE Harrison's 22e — Ch 13 Palliative and End-of-Life Care, §Futile Care; §Euthanasia and Physician-Assisted Suicide; §Legal Aspects — pp. 89–90

Definition

- **Euthanasia:** intentionally administering medications or other interventions to cause a patient's death. Consent status defines the type.
- **Physician-assisted suicide (PAS):** a physician provides medications or other interventions, understanding that the patient can use them to end their own life.
- In PAS the patient performs the final act. In euthanasia the clinician administers the agent.
- Stopping life-sustaining treatment and giving opioids for pain or dyspnoea are long-established as ethical (medical profession) and legal (courts). They are not euthanasia or PAS.
- Some US advocates prefer the term physician-assisted death (PAD). This is not accepted in many countries, and the terms are used inconsistently.
 - Netherlands: PAD means terminating life-sustaining treatment, such as a ventilator.
 - UK: PAD means prescribing life-ending drugs to the terminally ill. PAS means the same for patients who are not necessarily terminally ill.
 - Harrison's therefore uses the term PAS.

Types of euthanasia

Table 1: Types of euthanasia and PAS (Harrison's Table 13–8)

Term	Definition	Legal status
Voluntary active euthanasia	Deliberately giving drugs or interventions to cause death, with the patient's informed consent	Netherlands, Belgium, Luxembourg, Canada, Colombia, Spain, Western Australia, New Zealand
Involuntary active euthanasia	Deliberately causing death when the patient was competent to consent but did not consent (e.g. was not asked)	Nowhere
Passive euthanasia	Withholding or withdrawing life-sustaining treatment to let the patient die	Everywhere
Physician-assisted suicide	Physician supplies drugs that the patient can use to end life	Netherlands, Belgium, Luxembourg, Canada, Colombia, Germany, Switzerland and several US states

Table 13-8 — Harrison's 22e, pr.89. TABLE 13-8 Definitions of Physician-Assisted Suicide and Euthanasia

%	TERM	DEFINITION	LEGAL STATUS
es	Voluntary active euthanasia	Intentionally administering medications or other interventions to cause the patient's death with the patient's informed consent	Netherlands, Belgium, Luxembourg, Canada, Colombia, Spain, Western Australia, New Zealand
ts	Involuntary active euthanasia	Intentionally administering medications or other	Nowhere
in			
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- Active euthanasia: the clinician acts to end life.
- Passive euthanasia is the ethically accepted withholding or withdrawal of treatment, which is routine practice (for example, ventilator withdrawal).

Legal aspects

- Euthanasia and PAS are legal in the Netherlands, Belgium, Luxembourg, Colombia, Canada, Spain, Portugal, Western Australia and New Zealand.
- Spain (2021) and Portugal (2023) are the most recent countries to legalise both.
- Switzerland and Germany: a layperson can legally elect assisted suicide under certain conditions.
- Northern Territory (Australia) legalised euthanasia in 1996. The law was repealed 9 months later.
- USA: PAS is legal in Washington, D.C. and 10 states. No US state has legalised euthanasia.
- US criteria: terminal illness with **<6 months** prognosis, and eligibility determined through a process with a **15-day waiting period**.
- Netherlands and Canada do not require terminal illness. The key criterion is "unbearable suffering".

Practice and epidemiology

- Fewer than **10–20%** of terminally ill patients consider euthanasia or PAS for themselves.
- Use is rising but still rare. At most **5%** of deaths occur this way, even in the Netherlands and Belgium.
- Netherlands: 5.1% of deaths in 2022.
- Oregon: 0.82% of deaths in 2023.
- Washington: 0.53% of deaths in 2022.
- In Belgium, the Netherlands, Oregon and Washington, **>70%** of users have cancer.

Why patients request it

- Pain is not the primary motivator.
- Depression and hopelessness are strongly associated with interest in euthanasia or PAS.
- Depressed terminally ill cancer patients in the Netherlands were **four times** more likely to request euthanasia. Uncontrolled pain was not associated with greater interest.
- Commonest end-of-life concerns in Oregon and Washington: loss of autonomy, inability to enjoy activities, and fear of losing dignity.
- Oregon data also show growing feelings of being a burden and financial concerns.

Problems and concerns

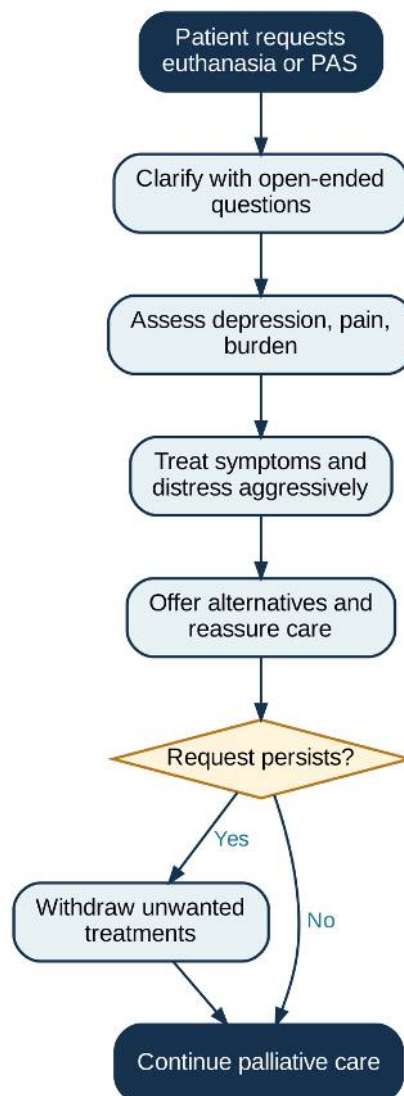
- Neither is guaranteed to be painless or quick. Technical problems occurred in up to **20%** of Dutch cases.
 - Examples: patients waking from coma, failing to become comatose, regurgitating the drugs, and prolonged time to death.
- Oregon and Washington PAS data: median time from ingestion to coma was 5 min, and to death 25 min. The longest time to death was 104 h.

- Some Oregon cases appear "transactional". The average prior physician–patient relationship fell from 18 weeks to 5 weeks. Fewer than 1% of patients had formal psychiatric assessment before prescription.
- Cases have been reported of providers actively encouraging patients to use these interventions.

Approach to a patient who requests euthanasia or PAS

- Clarify the request using empathic, open-ended questions, e.g. "What makes you want to consider this option?".
- Avoid expressing either moral opposition or moral support. Both can seem judgemental or imply that the patient's life is worthless.
- Reassure the patient of continued care and commitment.
- Educate about alternatives: symptom management and withdrawal of unwanted treatments.
- Correct misconceptions about how effective euthanasia is and about its legal implications.
- Assess and treat depression, hopelessness, psychological distress, physical suffering and economic burden aggressively.
- After clarification, most patients choose another approach, such as declining life-sustaining interventions. This may include refusing nutrition and hydration.

Flowchart 1: Responding to a request for euthanasia or PAS



Related: withdrawal of life support (passive euthanasia)

- Before ventilator withdrawal, stop neuromuscular blockers. Give sedatives and analgesics so that discomfort is visible and can be treated.

- Common practice: midazolam 2–4 mg or lorazepam 2–4 mg bolus, then morphine 5–10 mg bolus, then a morphine infusion at 50% of the bolus dose per hour.
- For heavy airway secretions: IV scopolamine 100 µg/h.
- Median time to death after stopping the ventilator is 1 h. Up to 10% survive for 1 day or more.

PEARLS

- Euthanasia: the clinician administers the agent. PAS: the patient takes the agent that the physician supplied.
- Types: voluntary active, involuntary active, passive. Involuntary active euthanasia is legal nowhere; passive is accepted everywhere.
- Withholding or withdrawing life support, and opioids for symptom relief, are not euthanasia.
- No US state has legalised euthanasia. US PAS needs a prognosis of <6 months and a 15-day wait.
- The Netherlands and Canada require unbearable suffering, not terminal illness.
- Depression and hopelessness drive requests more than pain does.
- Up to 20% of Dutch euthanasia or PAS cases had technical problems.
- A request is an opportunity to explore suffering. Do not endorse or oppose it.

7. Palliative care — domains, P-SPIKES, symptoms of the terminally ill and advance care planning

ASKED 3* · Long answer

Asked in: Jun 2021 P-I Q5 (10 marks) · Jun 2022 P-I Q4(a) (2 marks) · Jun 2022 P-I Q4(b) (3 marks) · Jun 2025 P-IV Q6(a) (4 marks) · Jun 2025 P-IV Q6(b) (3 marks) · Jun 2025 P-IV Q6(c) (3 marks)

Q: Discuss about the four domains of quality palliative care and write down the elements of communicating bad news. [5+5] [10]

Q: What is the P-SPIKES Approach? [2]

Q: Discuss the various elements of this approach. [3]

Q: What is the P-SPIKES approach? [4]

Q: Enumerate the common symptoms of terminally ill patients. [3]

Q: Write about advance care planning in terminally ill patients for palliative management. [3]

SOURCE Harrison's 22e — Ch 13 Palliative and End-of-Life Care, §Hospice and the Palliative Care Framework; Continuous Goal Assessment; Interventions; Further Reading — pp. 76–77, 79, 92

Harrison's 22e — Ch 73 Approach to the Patient with Cancer, §Supportive Care — p. 505

Harrison's 22e — Ch 489 Caring for the Geriatric Patient, §Pathophysiology; End-of-Life and Palliative Care — p. 3894

[W1] MoHFW/DGHS — National Programme for Palliative Care (NPPC) Operational Guidelines — 2017 — <https://dghs.mohfw.gov.in/nppc.php>

[W2] Supreme Court of India — Common Cause v. Union of India (2018) 5 SCC 1, as modified by order dated 24 Jan 2023 — <https://ijmr.org.in/procedures-to-implement-the-supreme-court-of-india-directives-to-withdraw-withhold-life-sustaining-medical-treatment/>

Definition and framework of palliative care

- Palliative care is an **interdisciplinary team approach**. It covers pain and symptom management, spiritual and psychological care for the patient, and support for family caregivers during the illness and bereavement.
- Palliative care is started **many months before death** to focus on symptom relief. Hospice follows in the last few months.
- Early introduction avoids leaving hospice until the very end. It gives patients and families time to accommodate and transition.
- Patients often receive palliative interventions long before they are formally labelled terminally ill, i.e. likely to die within 6 months.
- Providing optimal care means services must be available in many settings, especially non-institutional ones, because many serious conditions are now treated at home or as outpatients.
- Supportive care determines whether patients continue curative therapy and is a major determinant of quality of life.
- The oncology credo is to cure sometimes, to extend life often and to comfort always.
- Palliative care is cost-effective when delivered in an organised fashion.

Four domains of quality palliative care

- Quality palliative and end-of-life care rests on four broad domains:
 - **Physical symptoms**
 - **Psychological symptoms**
 - **Social needs**, including interpersonal relationships, caregiving and economic concerns
 - **Existential or spiritual needs**
- A comprehensive assessment evaluates all four domains. It is a modified medical history and examination that stresses both physical and psychological symptoms.
- The questions aim to find symptoms, sources of suffering and the degree to which symptoms interfere with quality of life.
- Assessment should be standardised and repeated to judge the effect of interventions.

Assessment tools

- Shorter validated instruments are preferred:
 - Revised **Edmonton Symptom Assessment Scale**
 - Condensed Memorial Symptom Assessment Scale (MSAS)
 - MD Anderson Brief Symptom Inventory
 - Rotterdam Symptom Checklist
 - Symptom Distress Scale
 - PROMIS and the ISAAC tool
- Mental health: **PHQ-9** screens for depression and **GAD-7** for anxiety. This stops the assessment from focusing only on pain.
- Invasive tests are best avoided. Even minimally invasive tests need a benefit-to-burden check.
- Uncomfortable parts of the examination that will not change management should be omitted.
- **Social needs**: ask about close relationships, financial burden, caregiving needs and access to care.
- **Existential needs**: assess distress, emotional and existential well-being, and whether the patient has found purpose or meaning.
- **Perception of care**: ask about respect, clarity of information and whether care fits the patient's goals.

Communicating bad news – P-SPIKES approach

What it is

- "Bad news" situations are emotionally charged, potentially conflict-creating moments that need empathic communication.
- These moments include:
 - sharing a terminal diagnosis
 - discussing prognosis and treatment failure
 - shifting emphasis from cure to palliation
 - advance care planning
 - the patient's death
- Other frameworks exist: GUIDE, BREAKS, SHARE, ABCDE and the Serious Illness Conversation Guide.
- **SPIKES** is the oldest and most commonly used of these, a six-step process.
- **P-SPIKES** adds a preparatory step before the six steps. Harrison's Table 13-2 adapts it from Buckman, 1992.
- Good communication can lead to earlier hospice referral rather than overly aggressive treatment. It improves quality of life and the bereavement process.
- Families care about the setting of the discussion as well as the physician's preparation. In one study, 27% of ICU families wanted a more private space.

Table 13-2 — Harrison's 22e, pr.77. TABLE 13-2 Elements of Communicating Bad News—The P-SPIKES Approach

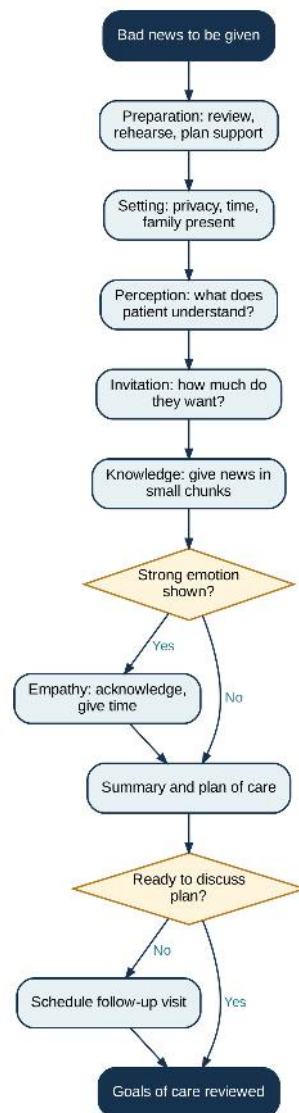
ACRONYM	STEPS	AIM OF THE INTERACTION	PREPARATION
P	Preparation	Mentally prepare for the interaction with the patient and/or family.	Review what Plan how you Rehearse key
S	Setting of the interaction	Ensure the appropriate setting for a serious and potentially emotionally charged discussion.	Ensure that p Devote suffic Ensure privac Bring a box o
P	Patient's perception and preparation	Begin the discussion by establishing the baseline and whether the patient and family can grasp the information. Ease tension by having the patient and family contribute.	Start with ope Possible ques <i>What do yo When you What did E What do yo</i>
I	Invitation and information needs	Discover what information needs the patient and/or family have and what limits they want regarding the bad information.	Possible ques <i>If this conc Would you you like me</i>
K	Knowledge of the condition	Provide the bad news or other information to the patient and/or family sensitively.	Do not just du Check for pat Possible phra <i>I feel badly Unfortunat I'm afraid t</i>
E	Empathy and exploration	Identify the cause of the emotions—e.g., poor prognosis. Empathize with the patient's and/or family's feelings. Explore by asking open-ended questions.	Strong feeling Acknowledge Remind them Give them tim Remind the p Possible phra <i>I imagine t You look ve I wish the We'll do w.</i>
S	Summary and planning	Delineate for the patient and the family the next steps, including additional tests or interventions.	It is the unkno with goals an accept (or rej If the patient follow-up visi

Source: Adapted from R Buckman: *How to Break Bad News: A Guide for Health Care Professionals*.

Table 1: Elements of the P-SPIKES approach

Step	Aim	Key actions or phrases
P Preparation	Mentally prepare	Review the information, plan emotional support, rehearse key phrases
S Setting	Suitable setting	Patient, family and supports present; enough time; privacy; no interruptions; tissues
P Patient's perception	Establish baseline understanding	Open-ended questions, e.g. "What do you understand about your illness?"
I Invitation	Find information needs and limits	"Do you want to know?"; ask who else should be told
K Knowledge	Give the news sensitively	Do not dump information; check understanding; use warning phrases
E Empathy and exploration	Identify and acknowledge emotions	Open questions; feelings are normal; give time; promise not to abandon
S Summary and planning	Set out next steps	Schedule with goals and landmarks; give rationale; follow-up if not ready

Flowchart 1: P-SPIKES sequence



Points of emphasis

- The patient's perception step starts with open-ended questions. This eases tension by letting the patient and family contribute.
- Invitation lets the patient set limits on what they want to know.

- In the knowledge step, check family understanding. Use phrases such as "I'm afraid the news is not good".
- Empathy requires acknowledging that strong reactions are normal, even if frightening.
- Uncertainty increases anxiety, so the summary recommends a schedule with goals and landmarks.

Continuous goal assessment

- The main barriers are the difficulty of accurate prognosis and emotional resistance to accepting a poor prognosis.
- The solution is to integrate palliative care months before the final 6 months. It then no longer conveys failure or "giving up hope".
- Goal assessment should be part of routine reassessment at most encounters.
- Goals range from cure, to prolonging life, to symptom relief, to peace of mind, to dying in a way that leaves loved ones with positive memories.
- The **seven-step protocol** for discerning goals:
 - Ensure information is complete and understood.
 - Explore hopes and identify realistic goals.
 - Share all options.
 - Respond with empathy.
 - Make a plan for the realistic goals.
 - Follow through.
 - Review periodically and revise.
- The steps need not be followed in rote order.

Common symptoms of terminally ill patients

- Pain assessment is often called the "fifth vital sign". Data show this has not improved pain management.
- Good palliative care requires much more than good pain management.
- The most common symptoms in all terminally ill patients are **pain, fatigue, insomnia, anorexia, dyspnoea, depression, anxiety, nausea and vomiting**.
- In the last days of life, **terminal delirium** and **excessive secretions** are common.
- Patients with advanced cancer have an average of **11.5** physical and psychological symptoms.
- About 70% of cancer patients develop dyspnoea preterminally.

Table 13-4 — Harrison's 22e, pr.79. TABLE 13-4 Common Physical and Psychological Symptoms of Terminally Ill Patients

	PHYSICAL SYMPTOMS	PSYCHOLOGICAL SYMPTOMS
1g i-	Pain	Anxiety

Table 2: Common symptoms of terminally ill patients

Physical	Psychological
Pain	Anxiety
Fatigue and weakness	Depression
Dyspnoea	Hopelessness
Insomnia	Meaninglessness
Dry mouth	Irritability
Anorexia	Impaired concentration
Nausea and vomiting	Confusion
Constipation	Delirium
Cough	Loss of libido
Swelling of arms or legs	
Itching	

Physical	Psychological
Diarrhoea	
Dysphagia	
Dizziness	
Faecal and urinary incontinence	
Numbness or tingling in hands or feet	

- Non-pharmacological pain treatment and identification of psychosocial risk factors for addiction are now recommended (Joint Commission, 2017).
- Non-pharmacological measures for insomnia include sleep hygiene and stimulus-control therapy.

Advance care planning (ACP)

Process

- ACP elicits the patient's preferences for interventions in defined scenarios, e.g. a persistent vegetative state.
- The patient and proxy each complete the worksheet for the other, and may involve other family members.
- At a return visit, the provider checks the preferences and resolves inconsistencies.
- The document is signed by the patient and proxy, filed in the chart, and copied to relevant family members and care sites.
- Preferences change, so documents must be **reviewed periodically**.
- Wishes should be elicited before the terminal phase and reviewed periodically.
- Internists should be proactive in encouraging advance directives **before a health-care crisis**.
- In older patients, limited life expectancy is a critical factor in end-of-life decisions.

Types of documents

- **Living will** (instructional directive): an advisory document describing the decisions that should direct care.
 - It can be disease-specific, e.g. for cancer, renal failure or HIV.
 - Less specific forms are general statements, e.g. refusing life-sustaining interventions.
- **Health care proxy** (durable attorney for health care): a person chosen by the patient to make decisions.
- The two are often **combined**. The directive must state whether the patient's preferences or the proxy's choice prevails in a conflict.
- **POLST** is a colour-coded form that follows the patient across care settings.
- Statutory documents fulfil state law and advisory documents reflect the patient's wishes. Both are legal.

Geriatric and end-of-life decisions

- CPR survival in hospitalised patients aged 65 or older is <20%. In nursing-home residents it is almost zero, so CPR is futile for most of them.
- Enteral feeding tubes should not be placed in end-stage dementia.
- Advanced dementia should be considered a terminal illness.
- If reversibility is in doubt, the patient's wishes determine the level of care.
- Discussions should be candid, with clear informed consent, second opinions and documentation.

India: programme and legal framework

GUIDELINE

India: MoHFW/DGHS — National Programme for Palliative Care (NPPC) Operational Guidelines — 2017; Supreme Court of India — Common Cause v. Union of India (2018) 5 SCC 1, modified by order of 24 Jan 2023 · International: Harrison's 22e, ch. 13

- **NPPC objectives:**
 - Provide basic palliative care at district level.

- Build capacity in infrastructure, equipment and human resource.
- Promote community awareness.
- Broad-base palliative care into other programmes.
- The NPPC district team is **one physician, four nurses and one multi-task worker**.
- Each district hospital should have an exclusive **10-bedded palliative care ward**.
- Opioid prescribing and dispensing are restricted to authorised persons under the **NDPS (Third Amendment) Rules 2015**.
- **Common Cause 2018** upheld the right to life with dignity of a terminally ill patient. It legally recognised advance medical directives (living wills).
- The **Jan 2023 modification** replaced the 3-tier procedure with a 2-tier one:
 - A hospital primary board responds within **48 h**.
 - A secondary board, with at least two subject experts and one nominee of the District CMO, reviews its decision.

Table 3: Advance directives – India versus Harrison's

India: Supreme Court, Common Cause v. Union of India, 2018 (modified 2023)	International: Harrison's 22e, ch. 13 (US law)
Living will legally recognised by Supreme Court ruling	Living wills are governed by state statute; 48 states and DC had legislation as of 2024
Withdrawal or withholding is decided by a hospital primary board and a secondary board	Competent patients have a constitutional right to refuse or stop life-sustaining treatment (Cruzan); incompetent patients can exercise it only through "clear and convincing evidence" of prior wishes, e.g. an advance directive
Framework is judge-made, resting on Supreme Court judgments and guidelines; there is no parliamentary statute in India	Proxy laws exist in all states except Alaska

Care in the last days and after death

- Reassure the family that the patient is not suffering. This may need repeating.
- Hearing and touch are said to be the last senses lost. Encourage the family to talk to and touch the patient.
- For death at home, teach the family the cardinal signs of death:
 - cessation of cardiac function and respiration
 - fixed pupils
 - a cool body
 - muscle relaxation
 - possible incontinence
 - eyes may stay open
- Give the family a contact plan (hospice, covering physician or on-call palliative team). Without one, panic may trigger unwanted resuscitation and admission.
- A bereavement card or letter from the team is meaningful.
- Death of a spouse predicts poor health and mortality in the survivor, so alert the spouse's physician.
- Carers may develop burnout, with fatigue, disengagement and loss of fulfilment.

PEARLS

- Four domains: physical, psychological, social and existential or spiritual.
- P-SPIKES = Preparation, Setting, Patient's perception, Invitation, Knowledge, Empathy, Summary.
- SPIKES is a six-step process. P-SPIKES adds the preparation step.
- Ask "how much do you want to know?" before giving information.
- Advance directives are of two types, living will and health care proxy, and are often combined.
- Advance directives must be reviewed periodically.
- Symptoms most often present: pain, fatigue, insomnia, anorexia, dyspnoea, depression, anxiety, nausea and vomiting. Delirium and secretions are common in the last days.
- Use PHQ-9 and GAD-7 so that the assessment does not focus only on pain.
- India: living wills are recognised through Common Cause 2018. The 2023 modification created a 2-tier board with a 48-h response.
- NPPC district team = 1 physician + 4 nurses + 1 multi-task worker.

PART 2

Cardinal Manifestations and Presentation of Diseases

8. Pain pathways, pain modulation and drugs for neuropathic pain

ASKED 3* · Long answer

Asked in: Jun 2021 P-I Q4 (10 marks) · Jun 2022 P-I Q2(a) (2 marks) · Oct 2024 P-I Q2(a) (4 marks) · Oct 2024 P-I Q2(b) (3 marks)

Q: Discuss about the sensory pathways of the pain transmission and management of neuropathic pain. [5+5] [10]

Q: What is pain modulation? [2]

Q: What are peripheral and central mechanism for pain? [4]

Q: Enumerate drugs used for neuropathic pain. [3]

SOURCE Harrison's 22e — Ch 14 Pain: Pathophysiology and Management, §Neuropathic Pain, Treatment, Further Reading — pp. 96, 97, 100–101

Harrison's 22e — Ch 18 Low Back Pain — p. 124

Harrison's 22e — Ch 74 Symptom Control in Patients with Cancer, §Pain — p. 506

[W1] Soliman N, et al. (NeuPSIG) — Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis — Lancet Neurol 2025;24:413–428 — <https://pubmed.ncbi.nlm.nih.gov/40252663/>

Definition and scope

- **Pain** is processed along a chain: peripheral nociceptor, spinal transmission neuron, central nociceptive pathways, and a descending modulating circuit.
- **Pain modulation** is the regulation of pain-transmission neurons by modulatory circuits. These circuits can suppress pain or enhance it.
- **Neuropathic pain** is pain produced by damage to, or dysfunction of, peripheral or central nociceptive pathways.
- Lesions of these pathways usually cause loss or impairment of pain sensation. Paradoxically, they can also cause pain.
- This answer covers three linked parts:
 - the pathway and its peripheral and central mechanisms
 - pain modulation
 - neuropathic pain and its drugs

Sensory pathway of pain transmission

- **Peripheral pain fibres**
 - Nociceptive primary afferents carry the noxious signal from the periphery.

- They project to spinal pain-transmission neurons.
- **Central pathway**
 - Central nociceptive pathways pass through the spinal cord, brainstem and thalamus.
 - Injury at any of these levels can give central neuropathic pain.
- **Descending control**
 - Pain-inhibiting and pain-facilitating neurons in the medulla project to and control spinal pain-transmission neurons.
- **Clinical correlation of the pathway**
 - Pain in a damaged nerve is referred to the body region that nerve supplies.
 - A sensory deficit is characteristically co-extensive with the painful area.

Peripheral mechanisms of pain

- **Peripheral sensitization**
 - Primary afferent nociceptors become sensitized, so their threshold falls.
- **Damaged afferents**
 - They become highly sensitive to mechanical stimulation.
 - They may generate impulses with no stimulus (ectopic discharge).
- **Sodium channels**
 - Increased sensitivity and spontaneous activity are due, in part, to an increased density of **sodium channels** in the damaged fibre.
 - This is the basis for using sodium-channel-acting drugs (carbamazepine, lidocaine).
- **Adrenergic sensitivity**
 - Damaged afferents may develop sensitivity to **norepinephrine**.
 - Sympathetic outflow can then activate damaged nociceptors.
- **Sympathetic activation of intact nociceptors**
 - When inflammation is present, sympathetic activity can activate undamaged nociceptors.

Central mechanisms of pain

- **Deafferented spinal neurons**
 - Spinal pain-transmission neurons cut off from their normal input become spontaneously active.
- **Combined hyperactivity**
 - Both central and peripheral nervous system hyperactivity contribute to neuropathic pain.
- **Central lesions**
 - Trauma or vascular injury to the spinal cord, brainstem or thalamus can produce central neuropathic pain.
- **Central facilitation**
 - Pain-transmission neurons can be activated by modulatory neurons.
 - In theory, a pain signal can therefore arise with no peripheral noxious stimulus.
 - Functional imaging shows increased activity in this circuit during migraine.
- **Psychological contribution**
 - A central facilitating circuit explains why pain can be induced by suggestion or enhanced by expectation.
 - It also explains how psychological factors contribute to chronic pain.
- **Central sensitization in nociplastic pain**
 - Nonspecific back pain is a nociplastic pain, with central sensitization as a risk factor.
 - It is bilateral, with diffuse tenderness and a nonfocal neurological examination.
 - Patients often score in the "neuropathic" range on painDETECT.

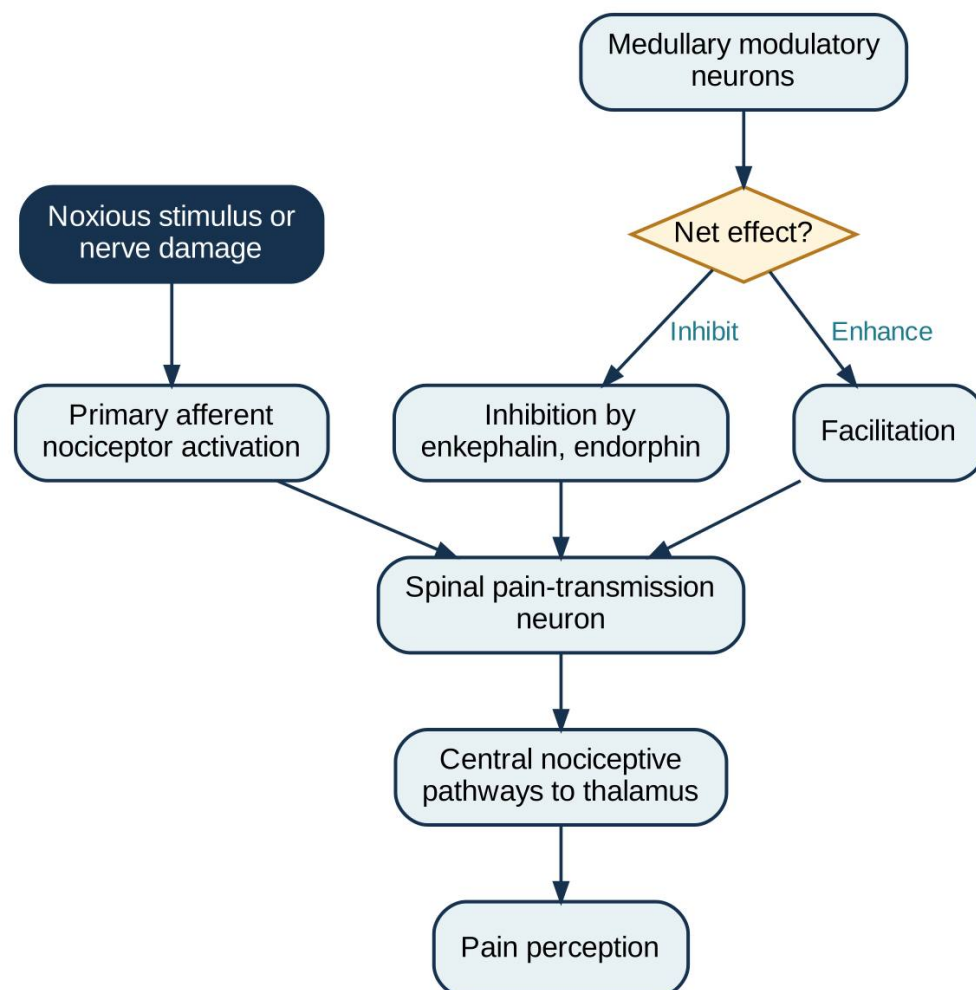
Table 1: Peripheral versus central mechanisms of pain

Feature	Peripheral	Central
Site	Primary afferent nociceptor	Spinal neuron, brainstem, thalamus, modulatory circuit
Key change	Sensitization, ↑ sodium channel density, adrenergic sensitivity	Spontaneous firing of deafferented neurons, facilitation
Result	Ectopic discharge, allodynia, sympathetically maintained pain	Pain without stimulus, expectation-driven pain, post-stroke pain
Drug target	Sodium channels, topical lidocaine, sympathetic block	Gabapentinoids, SNRIs, TCAs, opioids

Pain modulation

- **Definition:** it is the up- or down-regulation of spinal pain transmission by descending circuits.
- **Inhibition (analgesia)**
 - The descending modulatory system contains the opioid receptor and endogenous opioid peptides such as enkephalins and **β-endorphin**.
 - Reduced function of this system reduces the analgesic effect of systemic opioids such as morphine.
- **Activation of the endogenous opioid system**
 - The most reliable way is suggestion of pain relief.
 - Intense emotion directed away from the injury also works (severe threat, athletic competition).
 - Endogenous opioids are released after surgical procedures and with placebo.
- **Facilitation**
 - Medullary pain-facilitating neurons enhance transmission.
 - This is the basis of expectation-related and psychological enhancement of pain.

Flowchart 1: Pain pathway and modulation



Neuropathic pain: features and syndromes

- **Quality**
 - Pain is unusual: burning, tingling or electric shock-like.
 - It may be spontaneous, or triggered by very light touch.
- **Signs**
 - A sensory deficit coincides with the painful area.
 - **Hyperpathia** is a greatly exaggerated response to innocuous or mild nociceptive stimuli, especially when repeated.
 - **Allodynia** is pain evoked by the lightest moving stimulus.
- **Examples**
 - Diabetic neuropathy and herpes zoster (postherpetic neuralgia) are examples.
 - Spinal cord, brainstem or thalamic injury causes central pain.
- **Course:** it is often severe and resistant to standard treatments for pain.
- **Complex regional pain syndrome (CRPS)**
 - It begins after a delay of hours to weeks, with burning pain, swelling, periarticular bone loss and arthritic change.
 - **Type II** (causalgia) follows an identifiable nerve injury.
 - **Type I** (reflex sympathetic dystrophy) has no obvious nerve injury.
 - Early pain may be relieved by a local anaesthetic sympathetic block.
- **Painful radiculopathy:** in herniated disc, pain radiates in a dermatomal distribution and straight leg raising is usually positive.
- **Neuropathy:** it is typically multidermatomal when advanced, with sensory and motor loss and diminished reflexes.

Management of neuropathic pain

GUIDELINE

International: IASP NeuPSIG — Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis — 2025 · Harrison's 22e, ch. 14

General principles

- Individualize treatment.
- Move quickly to give relief, and minimize drug side effects.
- Treat the cause where possible, and use non-drug measures where appropriate.
- No class has consensus as universal first-line treatment for any chronic pain.
- Drugs of different classes can be combined to optimize control.
- Allow adequate trials. The number needed to treat for neuropathic drugs ranges from 3 to 10, so 3–4 week trials of alternate drugs are needed.

Stepwise drug approach (NeuPSIG)

- **First line:** TCAs, SNRIs (duloxetine, venlafaxine) and alpha-2-delta ligands (pregabalin, gabapentin) received a strong recommendation (NeuPSIG 2025).
 - Caution is advised with most TCAs.
- **Second line:** capsaicin 8% patch, lidocaine 5% plaster and capsaicin cream received a weak recommendation (NeuPSIG 2025).
- **Third line:** botulinum toxin A, rTMS and opioids (including tramadol) received a weak recommendation (NeuPSIG 2025).
- **Combination therapy**
 - It is used when a single drug is inadequate.
 - Gabapentin plus nortriptyline or morphine was superior to monotherapy in two trials.

Harrison's approach

- **Topical lidocaine**
 - A 5% patch is effective in postherpetic neuralgia with prominent allodynia.
 - It gives immediate relief without side effects.
- **First-line oral drugs:** gabapentin, pregabalin, or antidepressants (nortriptyline, desipramine, duloxetine, venlafaxine).
- **Elderly and mentally active patients**
 - Relatively high anticonvulsant doses are needed, so sedation is common.
 - TCAs also sedate, but SNRIs sedate much less.
 - SNRIs should therefore be first-line in the elderly and in patients whose daily activities need high-level mental activity.
- **Opioids**
 - They are second- or third-line.
 - They sedate, and their effect lessens over time, leading to dose escalation and occasionally worsening pain.
- **Tramadol and tapentadol**
 - Both have mixed opioid and norepinephrine reuptake action.
 - Tapentadol is the stronger opioid, with action enhanced by norepinephrine reuptake blockade.
- **Antiarrhythmics**
 - Lidocaine infusion relieves pain for only hours after it stops.
 - Oral mexiletine is poorly tolerated, with frequent GI effects.
- **Cancer neuropathic pain**
 - Opioids help neuropathic pain as much as gabapentin or nortriptyline, and the combination is more effective.
 - Relief, if it occurs, appears within 4–8 days.
- **Gabapentinoids in radicular pain**
 - Systematic reviews show minimal benefit against harms such as dizziness, somnolence and gait disturbance.
- **Interventional options:** epidural steroid injections are most effective in the acute phase of disc-related radicular pain.
- **CRPS:** acute pain and inflammatory signs can be rapidly relieved by blocking the sympathetic nervous system.

Table 14-1 — Harrison's 22e, pr.97. TABLE 14-1 Drugs for Relief of Pain

GENERIC NAME	DOSE, mg	INTERVAL	
Nonnarcotic Analgesics: Usual Doses and Intervals			
Acetylsalicylic acid	850 PO	q4h	
Acetaminophen	650 PO	q4h	
Ibuprofen	400 PO	q4–8h	
Naproxen	250–500 PO	q12h	
Fenoprofen	200 PO	q4–6h	
Indomethacin	25–50 PO	q6h	
Ketorolac	15–60 IM/IV	q4–8h	
Celecoxib	100–200 PO	q12–24h	
Valdecoxib	10–20 PO	q12–24h	
GENERIC NAME	PARENTERAL DOSE, mg	PO DOSE, mg	
Narcotic Analgesics: Usual Doses and Intervals			
Codeine	30–60 q4h	30–60 q4h	
Oxycodone	—	5–10 q4–8h	
Oxycodone extended-release	—	10–40 q12h	
Morphine	5 q4h	30 q4h	
Morphine sustained release	—	15–60 bid to tid	
Hydromorphone	1–2 q4h	2–4 q4h	
Levorphanol	2 q6–8h	4 q6–8h	
Methadone	5–10 q6–8h	5–20 q6–8h	
Meprobamate	50–100 q3–4h	300 q4h	
Butorphanol	—	1–2 q4h	
Fentanyl	25–100 µg/h	—	
Buprenorphine	5–20 µg/h	—	
Buprenorphine	0.3 q6–8h	—	
Tramadol	—	50–100 q4–8h	
GENERIC NAME	UPTAKE BLOCKADE	SEDATIVE POTENCY	ANTICHOLIN POTENCY
	5-HT	NE	
Antidepressants ^a			
Doxepin	++	+	High
Amiripryline	+++	++	High
Imipramine	+++	++	Moderate
Nortriptyline	+++	++	Moderate
Desipramine	+++	+++	Low
Venlafaxine	+++	++	Low
Duloxetine	+++	+++	Low
GENERIC NAME	PO DOSE, mg	INTERVAL	
Anticonvulsants and Antiarrhythmics ^a			
Carbamazepine	200–300	q6h	
Oxcarbazepine	300	bid	
Gabapentin ^a	600–1200	q8h	
Pregabalin	150–600	q8h	

^aAntidepressants, anticonvulsants, and antiarrhythmics have not been approved by the FDA for postherpetic neuralgia.

Abbreviations: GI, gastrointestinal; 5-HT, serotonin; NE, norepinephrine; NSAID, nonsteroidal anti-inflammatory drug.

Drugs used for neuropathic pain

- **Antidepressants**
 - TCAs: amitriptyline, nortriptyline, imipramine, desipramine, doxepin.
 - SNRIs: duloxetine, venlafaxine.
 - SSRIs such as fluoxetine are much less effective for pain.
- **Anticonvulsants**
 - Carbamazepine, oxcarbazepine, phenytoin.
 - Gabapentin and pregabalin, which are calcium channel alpha-2-delta subunit ligands.
- **Topical agents:** 5% lidocaine patch; capsaicin.
- **Opioids and mixed agents:** tramadol, tapentadol, morphine, oxycodone.
- **Antiarrhythmics:** lidocaine and mexiletine are less likely to be effective.

Table 2: Drugs for neuropathic pain, with doses and comments (Harrison's Table 14-1)

Drug	Dose	Comment
Amitriptyline	Average 150 mg/d (25–300)	Highest anticholinergic potency; arrhythmia risk
Nortriptyline	Average 100 mg/d (40–150)	Moderate sedation; low orthostatic hypotension
Desipramine	Average 150 mg/d (50–300)	Low sedation
Duloxetine	Average 40 mg/d (30–60)	No anticholinergic effect, orthostatic hypotension or arrhythmia
Venlafaxine	Average 150 mg/d (75–400)	Same favourable profile as duloxetine
Carbamazepine	200–300 mg q6h	Rare aplastic anaemia, hepatotoxicity
Oxcarbazepine	300 mg bid	Similar to carbamazepine
Gabapentin	600–1200 mg q8h	Dizziness, GI irritation; useful in trigeminal neuralgia
Pregabalin	150–600 mg bid	Dry mouth, oedema

- Gabapentin is FDA approved up to 1800 mg/d for postherpetic neuralgia.

Table 14-2 — Harrison's 22e, pr.100. TABLE 14-2 Painful Conditions That Respond to Tricyclic Antidepressants

Postherpetic neuralgia^a
 Diabetic neuropathy^a
 Fibromyalgia^a
 Tension headache^a
 Migraine headache^a
 Rheumatoid arthritis^{a,b}
 Chronic low back pain^b
 Cancer
 Central poststroke pain

^aControlled trials demonstrate analgesia. ^bControlled studies indicate benefit but not analgesia.

Drug-specific points

- **TCAs**
 - They are effective in postherpetic neuralgia and diabetic neuropathy.
 - Their side effects are particularly problematic in the elderly.
 - They are additive to the side effects of opioids.

- **Venlafaxine and duloxetine**
 - They block both serotonin and norepinephrine reuptake.
 - They retain most of the pain-relieving effect of TCAs, with a side-effect profile like that of SSRIs.
 - They have largely supplanted TCAs in chronic pain.
- **Carbamazepine and phenytoin**
 - They relieve trigeminal neuralgia, a brief, shooting, electric shock-like pain.
 - Anticonvulsants help lancinating pain in particular.
- **Gabapentin and pregabalin**
 - They are effective across a broad range of neuropathic pains.
 - Their favourable side-effect profile makes them frequent first-line agents.
- **Cannabinoids:** analgesic effects are modest. They more consistently reduce the unpleasantness of pain.

Table 18-3 — Harrison's 22e, pr.123. TABLE 18-3 Clinical Evaluation, Diagnosis, and Treatment of Low Back Pain Etiologies

TABLE 18-3 Clinical Evaluation, Diagnosis, and Treatment of Low Back Pain Etiologies						
ETIOLOGY	RISK FACTORS	TYPICAL ONSET	CLINICAL PRESENTATION	PHYSICAL EXAM	DIAGNOSTIC TESTS	TREATMENTS ^a
Mechanical Pain						
Myofascial pain	Strenuous activities, sedentary lifestyle, abrupt movements (sneezing)	Usually insidious (chronic) but sometimes acute (muscle tear or spasm)	Axial pain, occasionally referred into thigh, mid-back, or groin. Often superimposed with other etiologies.	Tenderness, occasionally trigger points. Midline tenderness in between spinous processes may indicate ligamentous injury.	Occasionally ultrasound or electromyography	Pharmacologic: NSAIDs; nonbenzodiazepine muscle relaxants; antidepressants (e.g., duloxetine, tricyclic compounds); topical analgesics (e.g., diclofenac, lidocaine in those with irritable nociceptors or allodynia). Interventional: trigger point injections
Intervertebral disks	Advanced age (although patients younger than those with facet joint pain), acute (torsional event) or repetitive trauma, genetic predisposition	Insidious, occasionally abrupt (e.g., annular tear)	Axial pain, may radiate into extremities, more likely to be bilateral than SI or facet joint pain, worse with sitting	Midline tenderness, reduced range of motion (especially forward flexion)	Discography (high false-positive rate), bony vibration test; MRI generally nonspecific but high-intensity zone correlates with discography results	Pharmacologic: NSAIDs; antidepressants (e.g., duloxetine). Interventional: biacuplasty or IDET can be considered, but evidence for long-term benefit is mixed and disk puncture may increase risk of future disk degeneration; the benefit for intradiscal corticosteroid injections or ESI unclear
Vertebral fracture	Advanced age/osteoporosis, trauma	Abrupt (trauma) or insidious	Axial pain that may radiate into upper leg, worsened with activities	Midline tenderness	MRI to identify endplate abnormalities and acuity, plain films for acute fractures. Bony vibration test sometimes used.	Pharmacologic: NSAIDs; antidepressants (e.g., duloxetine), topical analgesics (e.g., diclofenac, lidocaine) only if superimposed soft tissue pain. Judicious use of opioids can be considered for severe pain secondary to acute fractures. Interventional: In acute vertebral compression fracture(s) (<6 weeks) with severe pain or disability, percutaneous vertebral augmentation (vertebroplasty or kyphoplasty) can be considered. The benefit for vertebral augmentation in chronic fractures is mixed. In patients with chronic axial pain with Modic type 1 or type 2 vertebral endplate/bone marrow changes on MRI and in whom other lumbar structures are less likely to be the predominant source of pain, basivertebral nerve RFA can be considered.
Facet joints	Increases with age, repetitive strain, genetic predisposition	Insidious	Axial pain may radiate into upper and occasionally lower legs. About half are bilateral.	Paraspinal tenderness, improved with sitting	CT or MRI generally reveals degeneration. Diagnostic medial branch or intraarticular injections.	Pharmacologic: NSAIDs; antidepressants (e.g., duloxetine). Interventional: RFA of the relevant medial branch nerves when preceded by a positive diagnostic block (e.g., 50% reduction in pain)
SI joint	Bimodal prevalence (younger individuals with unilateral extraarticular pathology often secondary to trauma, older people with bilateral intraarticular pathology). True and apparent leg length discrepancies, hip pathology, inflammatory arthritis (intraarticular), and lumbar spine surgery are predisposing factors.	Abrupt for extraarticular, insidious for intraarticular.	Unilateral (younger individuals, post-trauma) or bilateral (older individuals, intraarticular). About half of cases radiate into leg, sometimes below knee.	Tenderness below L5, positive provocative tests. Most painful area located near posterior superior iliac spine.	Advanced imaging (especially CT) may indicate intraarticular pathology. Battery of provocative tests correlate well with diagnostic injections.	Pharmacologic: NSAIDs; antidepressants (e.g., duloxetine), topical analgesics (e.g., diclofenac, lidocaine) only if superimposed soft tissue pain. Interventional: Intra- and/or extra-articular SI joint injection; RFA of the sacral lateral branch nerves for extraarticular pathology; minimally invasive fusion of the SI joint in refractory cases involving joint degeneration or instability
TABLE 18-3 Clinical Evaluation, Diagnosis, and Treatment of Low Back Pain Etiologies (Continued)						
ETIOLOGY	RISK FACTORS	TYPICAL ONSET	CLINICAL PRESENTATION	PHYSICAL EXAM	DIAGNOSTIC TESTS	TREATMENTS ^a
Predominantly Radicular Pain						
Herniated disk	Peak prevalence 30–50 years, preexisting disk degeneration, trauma, genetic predisposition, lifestyle (heavy lifting, smoking), obesity	Often abrupt, may be insidious	May be unilateral or bilateral (large, central herniation) pain radiating into leg in dermatomal distribution	Most patients also have back pain. Sensory loss and neurologic weakness common; may be associated with diminished reflexes. Straight leg raising test usually positive for lower lumbar levels.	MRI or CT scan, myelography when contraindicated. Fluoroscopic tests or selective nerve root blocks may be confirmatory.	Pharmacologic: NSAIDs; nonbenzodiazepine muscle relaxants; antidepressants (e.g., duloxetine). Gabapentinoids are commonly used (gabapentin, pregabalin), but systematic reviews and meta-analyses suggest minimal benefit when balanced against potential harms (e.g., dizziness, somnolence, gait disturbance). Interventional: ESIs, which are likely most effective in the acute phase of radicular pain secondary to disk herniation. ESIs might confer a weak but potentially meaningful surgery-sparing effect.
Spinal stenosis	Advanced age, concomitant spinal pathology (disk degeneration, spondylosis, facet hypertrophy)	Usually insidious	Usually unilateral for lateral recess or foraminal stenosis; central stenosis may be unilateral or bilateral. Wide-based gait, often affects multiple dermatomes. Pain often improves with sitting. Although the severity of pain and disability may wax and wane, the causes of spinal stenosis (e.g., spondylosis, degenerative changes/osteophyte formation) often progress with age.	Sensory and motor deficits; SLR test usually negative. Improved walking ability when bending forward.	MRI or CT scan	Pharmacologic: NSAIDs; nonbenzodiazepine muscle relaxants; antidepressants (e.g., duloxetine). Gabapentinoids are commonly used (gabapentin, pregabalin), but systematic reviews and meta-analyses suggest minimal benefit when balanced against potential harms, especially in the elderly (e.g., dizziness, somnolence, gait disturbance). Interventional: ESIs commonly used and may confer short-term and sometimes intermediate-term benefit, but evidence for long-term benefit is mixed given the progressive pathology.
Neuropathy	Underlying neuropathic pain condition (e.g., herpes zoster, diabetic amyotrophy)	Generally insidious, acute for herpes zoster	Lumbosacral dermatomes less common with herpes zoster than thoracic dermatomes. Unilateral (herpes zoster), occasionally bilateral (advanced neuropathies). Advanced neuropathies usually multidermatomal.	Sensory and motor loss, diminished reflexes	Workup for underlying cause; advanced imaging may rule out disk pathology	Pharmacologic: gabapentinoids (gabapentin, pregabalin), antidepressants (e.g., SNRIs, TCAs), topical local anesthetics (e.g., lidocaine patches or creams), topical capsaicin. Other anticonvulsants (e.g., oxcarbazepine, lamotrigine) are occasionally used, but minimal evidence is available. Interventional: peripheral nerve blocks might confer analgesia, but evidence for long-term benefit is minimal or negative for certain conditions (e.g., PHN).
Nociplastic Pain						
Nonspecific back pain	Central sensitization, more common in females, peak age 20s to 50s, genetic predisposition	Usually insidious, but >20% report a physical or psychological inciting event	Bilateral, often involves other spinal regions, frequently radiates into legs. Most patients have other nociplastic and nonnociplastic pain conditions. High co-prevalence rate of mood disorders and sleep dysfunction.	Marked diffuse tenderness, provocative tests often positive but nonspecific, neurological exam nonfocal	Based on clinical presentation. Patients often score in "neuropathic" range on validated instruments (painDETECT); central sensitization inventory and conditioned pain modulation may confirm central sensitization.	Pharmacologic: NSAIDs; nonbenzodiazepine muscle relaxants; antidepressants (e.g., duloxetine), gabapentinoids (gabapentin, pregabalin), over-the-counter topical analgesics (e.g., diclofenac, lidocaine, menthol). Nonpharmacologic therapies (e.g., physical therapy, targeted exercise) should be prioritized.

Chronic opioid use in neuropathic pain

- Before starting opioids, explore other options and explain the risks.
- Tolerance and physical dependence are likely with long-term use.
- Opioid-induced hyperalgesia can occur.
- Mixed agonist–antagonist opioids (butorphanol, buprenorphine) can precipitate an abstinence syndrome in dependent patients.
- Constipation is virtually universal. It should be treated expectantly.
- CDC checklist for long-term opioid therapy
 - Set goals, and check that non-opioid therapy has been optimized.
 - Check PDMP data and a urine drug screen.
 - Reassess within 1–4 weeks.
 - Use the lowest effective dose, and reassess benefits and risks carefully before raising the dose to ≥ 50 MME/day (CDC 2022).
 - Avoid escalating to doses with diminishing returns, and offer naloxone whenever overdose risk is increased.

PEARLS

- Neuropathic pain is burning, tingling or electric-shock-like, with allodynia and hyperpathia. A sensory deficit coincides with the painful area.
- Peripheral mechanisms: $\uparrow$ sodium channel density in damaged afferents and new adrenergic sensitivity.
- Central mechanisms: spontaneously active deafferented spinal neurons and facilitation by medullary modulatory neurons.
- Pain modulation is mediated by enkephalins and β -endorphin. Placebo and suggestion activate it.
- Neuropathic pain first line: TCAs, SNRIs, pregabalin and gabapentin (strong). Second line: capsaicin 8% patch, lidocaine 5% plaster, capsaicin cream. Third line: botulinum toxin A, rTMS and opioids including tramadol (NeuPSIG 2025).
- SNRIs are preferred in the elderly because they cause less sedation.
- Carbamazepine is the drug of choice for lancinating trigeminal neuralgia.
- The 5% lidocaine patch suits postherpetic neuralgia with allodynia.
- Give each neuropathic drug a 3–4 week trial.
- CRPS I has no nerve injury and CRPS II has one. Sympathetic block relieves early pain.

9. Stroke units — components, types and protocol

ASKED 1* • Long answer

Asked in: Apr 2023 P-IV Q8 (10 marks)

Q: Describe components, types of stroke units and management protocol in a stroke unit. [3+2+5] [10]

SOURCE [W1] European Stroke Organisation — Recommendations to Establish a Stroke Unit and Stroke Center — Stroke journal — <https://www.ahajournals.org/doi/10.1161/strokeaha.112.670430>
[W2] AHA/ASA — 2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke — 2026 — <https://www.ahajournals.org/doi/10.1161/STR.0000000000000513>
[W3] Indian Stroke Association — Recommendations for the early management of acute ischemic stroke: consensus statement — 2018 — <https://stroke-india.org/Content/pdf/stroke.pdf>
[W4] AHA — Ideal Foundational Requirements for Stroke Program Development and Growth: Scientific Statement — <https://www.ahajournals.org/doi/10.1161/STR.0000000000000424>
[W5] European Stroke Organisation — Certification of stroke units and stroke centres — European Stroke Journal — <https://pmc.ncbi.nlm.nih.gov/articles/PMC6453203/>
[W6] Primary and Comprehensive Stroke Centers: History, Value and Certification Criteria — PMC — <https://pmc.ncbi.nlm.nih.gov/articles/PMC3779669/>
[W7] Comprehensive Stroke Centers (Joint Commission certification criteria) — PMC — <https://pmc.ncbi.nlm.nih.gov/articles/PMC3773071/>
[W8] A Global Health Perspective on the 2026 AHA/ASA Stroke Guidelines: Lessons from the Indian Health System — 2026 — <https://pmc.ncbi.nlm.nih.gov/articles/PMC13506147/>
[W9] AHA/ASA — Guideline in Action: General Supportive Early Management: Blood Pressure and Glucose; AHA/ASA — 2021 Guideline for the Prevention of Stroke in Patients With Stroke and TIA — 2021 — <https://www.ahajournals.org/doi/10.1161/STROKEAHA.125.053824> ; <https://www.ahajournals.org/doi/10.1161/STR.0000000000000375>

NOT IN TEXTBOOK

Searched in the textbook pages supplied (Ch 14 Pain, §Chronic Pain; Ch 354 MASLD, §Treatment of MASLD; Ch 359 Acute and Chronic Pancreatitis, §Nutritional Therapy; Ch 398 Disorders of the Adrenal Cortex) for: stroke unit, stroke care organisation, stroke team, thrombolysis, NIHSS. None of these pages covers stroke units. The answer below is therefore built from guideline and society sources.

Framework and current documents

- **Documents used:**
 - The ESO Stroke Unit Certification Committee defined requirements for ESO Stroke Units and Stroke Centres from RCT evidence, guidelines and expert consensus.
 - The AHA/ASA 2026 early-management guideline is the current international acute ischaemic stroke (AIS) guideline. It replaces the 2018 guideline and its 2019 update.
 - India: Indian Stroke Association (ISA) consensus statement on early management of AIS, 2018.
 - The AHA scientific statement on foundational requirements for stroke programmes gives stroke-unit structural and process components.
- **Question scope:** (a) components, (b) types, (c) management protocol (3 + 2 + 5 marks).

Definition and rationale

- A stroke unit is a dedicated stroke ward served by a multiprofessional team. Its important features include a dedicated stroke unit ward and a multiprofessional team.
- Acute organised stroke unit care has been called the backbone of the chain of care for stroke patients in Europe.
- Access to stroke units is still limited.
- Certification refers to the unit, not the department or hospital.
- Key features are trained personnel, diagnostic equipment, acute treatment and collaboration with other stroke caregivers.

Components of a stroke unit

- **The team:**
 - It includes physicians, nurses, physiotherapists, occupational therapists, speech and swallowing therapists, neuropsychologists where available, and social workers with a case manager.
 - The team must work together in an organised and systematic way.

- **Structure and monitoring:**
 - The unit has two functional parts run by one team. Segment A is acute monitoring. Segment B is the post-acute step-down unit.
 - Segment A needs at least 4 beds with 24-hour monitoring of ECG, blood pressure, O₂ saturation and temperature.
- **Imaging and hospital support:**
 - Modern multislice CT is needed. It should be multidetector, allowing non-invasive arteriography, venography and perfusion CT (≥64 slices recommended).
 - Access to MRI and 7/7 digital subtraction angiography is needed, but not necessarily on site. Laboratory 24×7, emergency department 24×7 and an on-site ICU are also needed.
- **Leadership and expertise:**
 - The director is a stroke-trained physician.
 - The team needs at least 2 stroke physicians.
 - One physician is on call round the clock and can be on site within 30 minutes.
- **Volume:** The unit admits an average of at least 200 stroke or TIA patients per year.
- **Rehabilitation links:** If the hospital has no rehabilitation beds, it needs a written agreement with a rehabilitation department or hospital.

Table 1: Stroke-unit components (ESO and AHA frameworks)

Domain	Requirement	Source
Space	Own physical space, signage, fixed bed number; overflow <5%	AHA
Medical lead	Vascular neurologist as medical director; physician cover 24 h/d, in person or remote	AHA
Nursing	1 RN to 3–4 patients; 1 RN to 2 for the first 24 h after reperfusion	AHA
Education	RNs and physicians ≥8 h/yr stroke education; therapists ≥2 h/yr	AHA
Scales	NIHSS used by RNs and physicians; discharge mRS for all patients	AHA
Rounds	Interprofessional rounds ≥3/wk; mobility rounds ≥3/d	AHA
Non-medical staff	Full-time physiotherapist, occupational therapist, speech and swallowing therapist, social worker	ESO
Audit	Local stroke register, written pathways, quality indicators	ESO

- NIHSS use and a discharge mRS are expected of every stroke unit.
- ESO certification forms share 7 main criteria: Lead, Personnel, General infrastructure, Investigations, Interventions and monitoring, Teaching/meetings/research, and Numbers/quality indicators.
- ESO stroke-unit criteria are organised into 7 fields of action: vital functions, early diagnostics, basic surveillance, stroke-specific therapy, general interventions, secondary prevention, and early mobilisation with rehabilitation.

Types of stroke units

- **ESO model:** There are two certification levels: ESO Stroke Units and ESO Stroke Centres. This corresponds to the primary and comprehensive stroke unit division.
- **Stroke Centre:** It meets all Stroke Unit requirements and adds more advanced diagnostic and therapeutic equipment, a larger staff and expertise in rare or complex stroke subtypes.
- **Criteria count:** There are 44 criteria for the Stroke Unit and 49 for the Stroke Centre.
- **US model:** the Brain Attack Coalition defined primary stroke centres. Comprehensive stroke centres were later certified from 2012.
- **Acute stroke-ready hospitals:** these are an AHA category below the primary centre.
- **Functional description:**
 - A primary stroke unit is usually restricted to IV thrombolysis.
 - A comprehensive centre manages all aspects of care, including mechanical thrombectomy.
- **Beyond comprehensive:** ESO notes a possible third tier, the neurovascular centre, covering the whole neurovascular spectrum. It has not been certified.

- **Mobile stroke unit:** this is an ambulance-based unit and part of the pre-hospital chain, not a ward. It is endorsed in the 2026 AHA/ASA guideline.

Table 2: Primary versus comprehensive stroke unit

Feature	Stroke unit (primary)	Stroke centre (comprehensive)
Reperfusion	IV thrombolysis	IV thrombolysis plus thrombectomy
CT	≥64-slice recommended	≥64-slice required
Staff	Min. 2 stroke physicians	Larger team
Case mix	Common stroke subtypes	Rare or complex subtypes
Neurointervention	Referral pathway	In-house, 24×7

- Table 2 sources: The 24×7 neurointervention row comes from the AHA/TJC comprehensive-centre criteria, in which a neurointerventional physician is available 24 hours a day, 7 days a week.

Organisation in the Indian setting

- Low-burden components are largely directly implementable: stroke awareness, prehospital assessment, prenotification, severity scoring, dysphagia screening, glucose monitoring and pragmatic BP protocols.
- In India, advanced perfusion imaging, mobile stroke units and EVT pathways remain largely infrastructure-constrained.
- Supportive-care bundles are protocol-driven and need little advanced technology.
- A basic Indian stroke unit therefore means a monitored bed area, CT, a trained team and written protocols. Thrombectomy is by referral.

Table 3: Divergence on IV thrombolysis in patients on DOACs

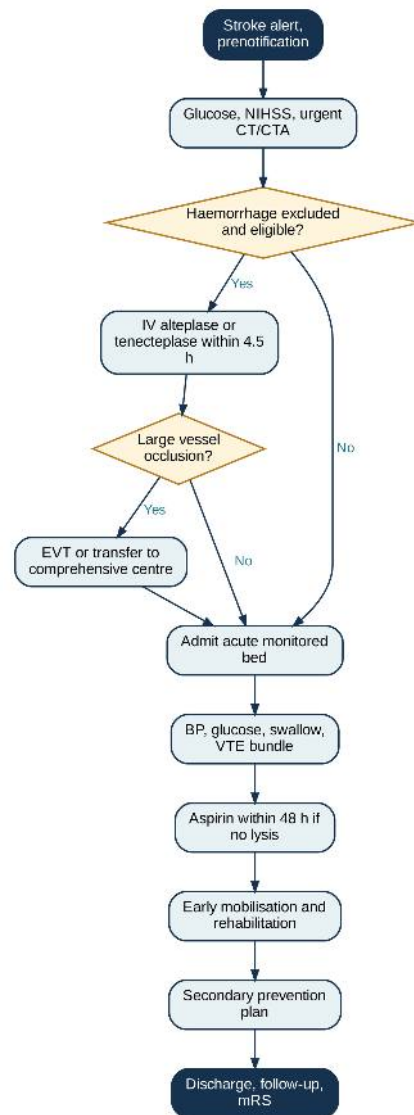
India: ISA, Early management of AIS consensus, 2018	International: AHA/ASA, 2026 Early Management of AIS (with US/European advice)
IVT in patients on DOACs is uncertain. Review TT, aPTT and PT for residual effect.	IVT within 48 h of last DOAC dose is advised against unless coagulation tests indicate safety.
Most centres cannot measure DOAC plasma levels.	Levels or specific assays guide decisions where available.

Management protocol in a stroke unit

GUIDELINE

India: Indian Stroke Association — Recommendations for the early management of acute ischemic stroke: consensus statement — 2018 · International: AHA/ASA — 2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke — 2026; AHA/ASA — 2021 Guideline for the Prevention of Stroke in Patients With Stroke and TIA — 2021; ESO — Recommendations to establish a stroke unit and stroke centre

Flowchart 1: Stroke-unit pathway from arrival to discharge



Hyperacute assessment

- Early brain imaging within 1 hour of admission is a quality indicator for patients arriving within 2 hours of onset.
- Vascular imaging is a quality indicator in ischaemic stroke or TIA.
- Check blood glucose before IVT. Severe hypo- and hyperglycaemia are defined as <50 and >400 mg/dL; correct them and reassess the deficit.
- When LVO imaging is needed for EVT selection, do not delay it for kidney function testing.

Reperfusion

- Either alteplase or tenecteplase is endorsed for IV thrombolysis within the 4.5-hour window.
- The 2026 guideline changes how thrombolysis contraindications are approached, and it gives expanded guidance for medium-vessel occlusions.
- Post-EVT patients stay in an ICU or step-down unit with frequent BP and neurological checks.

Monitoring and general supportive care

- **Monitoring:**
 - Continuous automated monitoring covers SpO₂, arterial BP, heart rhythm (1-lead ECG) and temperature. Blood glucose is checked intermittently.
 - Nursing includes positioning, pressure-area risk assessment, neurological scoring, fluid balance, excretion and temperature checks, and dysphagia assessment.
- **Blood pressure:**
 - After EVT, keeping BP at or below 180/105 mm Hg is reasonable (Class 2a, LOE B-NR).

- Avoid hypotension and large BP swings after reperfusion; they are linked to larger infarcts and worse outcome.
- Management is individualised, balancing cerebral and systemic perfusion, with an initial BP reduction of 15%.
- **Glucose:**
 - Intensive control to 80–130 mg/dL is not recommended; it does not improve outcome and raises the risk of severe hypoglycaemia.
 - Dysphagia screening is part of the 2026 update and is easily implemented.
- **Quality measures:**
 - Process measures include VTE prophylaxis within 48 hours of admission, antithrombotic by end of hospital day 2, statin at discharge, and rehabilitation considered.
 - Fever, oxygenation and VTE prophylaxis are largely protocol-driven.

Antithrombotic therapy

- Start aspirin within 48 hours in non-cardioembolic stroke, after imaging excludes haemorrhage.
- Triple antiplatelet therapy or anticoagulation gives no benefit and increases bleeding.
- Antiplatelet plus anticoagulant is typically not indicated. Long-term DAPT is not recommended.
- Short-term DAPT is for early minor stroke, high-risk TIA or severe symptomatic intracranial stenosis.

Rehabilitation and secondary prevention

- Early mobilisation begins in the stroke unit under the multiprofessional team.
- ESO requires a written early secondary-prevention protocol.
- The 2021 AHA/ASA prevention guideline groups recommendations by aetiological subtype.
- A Mediterranean-type diet is reasonable (COR 2a, LOE B-R).
- Discharge planning is done with the social worker. Outpatient rehabilitation follow-up is arranged.

Quality indicators and audit

- Every ESO unit works on at least 3 quality indicators.
- Keep a local register recording age, sex, initial severity, thrombolysis and discharge data.
- Record NIHSS on admission and mRS at discharge.
- Door-to-imaging and door-to-needle times are standard audit metrics.

PEARLS

- A stroke unit is a ward plus a team plus protocols, not just beds.
- ESO acute segment: **≥4 monitored beds**, with ECG, BP, SpO₂ and temperature monitoring.
- ESO volume threshold: **≥200 stroke/TIA admissions per year**; stroke physician on site within **30 min**.
- Two ESO levels: **Stroke Unit (primary, IV lysis)** and **Stroke Centre (comprehensive, EVT)**.
- AHA staffing: **1 RN: 3–4 patients, 1: 2** in the first 24 h after reperfusion.
- 2026 AHA/ASA: alteplase or tenecteplase in the **4.5 h** window; **no intensive glucose control to 80–130 mg/dL**.
- After EVT, keep BP **≤180/105 mm Hg** and avoid hypotension.
- Aspirin within **48 h** when no lysis; no triple antiplatelet therapy.
- India: DOAC and IVT is uncertain (ISA 2018); the limiting factor is infrastructure, not protocols.

10. Approach to a patient with chest pain

ASKED 1* · Long answer

Asked in: May 2024 P-I Q1 (10 marks)

Q: Discuss the approach to a patient with pain chest. [10]

SOURCE Harrison's 22e — Ch 15 Chest Discomfort, §Epidemiology; Other cardiopulmonary causes; Approach to the Patient — pp. 102, 104–106
 Harrison's 22e — Ch 284 Ischemic Heart Disease, §Prognosis — p. 2098
 Harrison's 22e — Ch 285 Non-ST-Segment Elevation Acute Coronary Syndrome — p. 2107
 [W1] ACC/AHA/ACEP/NAEMSP/SCAI — Guideline for the Management of Patients With Acute Coronary Syndromes — 2025 —
<https://www.jacc.org/doi/10.1016/j.jacc.2024.11.009>

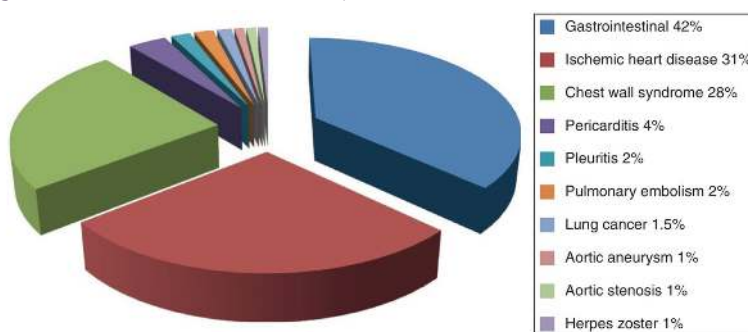
Definition and why it matters

- Chest discomfort is among the most common reasons for presenting to an emergency department (ED) or outpatient clinic.
- Causes are very varied, and only a minority are life-threatening conditions that must not be missed.
- In the US, it accounts for **6–7 million ED visits a year**. More than 60% are hospitalised for further testing.
- Fewer than 15% of those evaluated have acute coronary syndrome (ACS). Rates are 10–20% in most unselected series, and as low as 5% in some.
- A disconcerting **2–6%** of patients discharged with presumed non-ischaemic pain are later found to have had a missed myocardial infarction (MI).
- Routine liberal testing carries the risk of harm from unnecessary investigation.
- The approach therefore has two aims: rapid identification of high-risk conditions, and avoiding over-investigation.

Framework: three diagnostic categories

- Triage acute chest discomfort into three groups:
 - Myocardial ischaemia.
 - Other cardiopulmonary causes (myopericardial disease, aortic emergencies, pulmonary conditions).
 - Non-cardiopulmonary causes.
- The most common final diagnoses are gastrointestinal. Only about 5% are other life-threatening cardiopulmonary conditions.

Figure 15-1 — Harrison's 22e, pr.102. **FIGURE 15-1** Distribution of final discharge diagnoses in patients with nontraumatic acute chest pain. (Figure prepared from data in P Fruergaard et al: Eur Heart J 17:1028, 1996.)



- In many patients with transient pain, ACS is excluded but no cause is found.

Immediate stabilisation (acute ongoing pain)

- The first priorities are the patient's clinical stability and the probability of a life-threatening cause.
- High-risk conditions of principal concern:
 - ACS
 - Acute aortic syndrome
 - Pulmonary embolism
 - Tension pneumothorax
 - Pericarditis with tamponade

- Fulminant myocarditis also carries a poor prognosis, but usually presents with heart failure symptoms.
- Among non-cardiopulmonary causes, **oesophageal rupture** is the most urgent to diagnose.
- Significant tachycardia and hypotension are markers of important haemodynamic consequences. They should prompt a rapid survey for:
 - MI with cardiogenic shock
 - Massive pulmonary embolism
 - Tamponade
 - Tension pneumothorax
- Tension pneumothorax is a medical emergency in which trapped intrathoracic air causes haemodynamic collapse.
- Start monitoring and acquire a **12-lead ECG within 10 minutes of first medical contact** in suspected ACS (COR 1, LOE B-NR).
- A rapid targeted assessment is most relevant to patients with acute ongoing pain who present for emergency evaluation.
- Patients with chronic or resolved pain can have a general diagnostic assessment (outpatient evaluation).

Structured clinical questions

- Harrison's gives a four-step question series for structuring evaluation.

Table 1: Sequential questions in assessing chest discomfort

Step	Question	Examples
1	Acute, life-threatening, needs urgent evaluation?	Unstable IHD, aortic dissection, pneumothorax, pulmonary embolism
2	Chronic condition likely to cause serious complications?	Stable angina, aortic stenosis, pulmonary hypertension
3	Acute condition needing specific treatment?	Pericarditis, pneumonia/pleuritis, herpes zoster
4	Other treatable chronic condition?	Reflux, oesophageal spasm, peptic ulcer, gallbladder disease, cervical disc disease, costochondritis, anxiety

Table 15-2 — Harrison's 22e, pr.105. TABLE 15-2 Considerations in the Assessment of the Patient with Chest Discomfort

1. Could the chest discomfort be due to an acute, potentially life-threatening condition that warrants urgent evaluation and management?			
Unstable ischemic heart disease	Aortic dissection	Pneumothorax	Pulmonary embolism
2. If not, could the discomfort be due to a chronic condition likely to lead to serious complications?			
Stable angina	Aortic stenosis	Pulmonary hypertension	
3. If not, could the discomfort be due to an acute condition that warrants specific treatment?			
Pericarditis	Pneumonia/pleuritis	Herpes zoster	
4. If not, could the discomfort be due to another treatable chronic condition?			
Esophageal reflux	Cervical disk disease		
Esophageal spasm	Arthritis of the shoulder or spine		
Peptic ulcer disease	Costochondritis		
Gallbladder disease	Other musculoskeletal disorders		
Other gastrointestinal conditions	Anxiety state		

Source: Developed by Dr. Thomas H. Lee for the 18th edition of *Harrison's Principles of Internal Medicine*.

Focused history

- The history and examination direct all later testing.
- Assess **quality, location (including radiation), pattern (onset, duration), provoking/relieving factors and associated symptoms.**
- Quality of pain alone is never sufficient to make a diagnosis.
- Severity of discomfort has poor diagnostic accuracy.

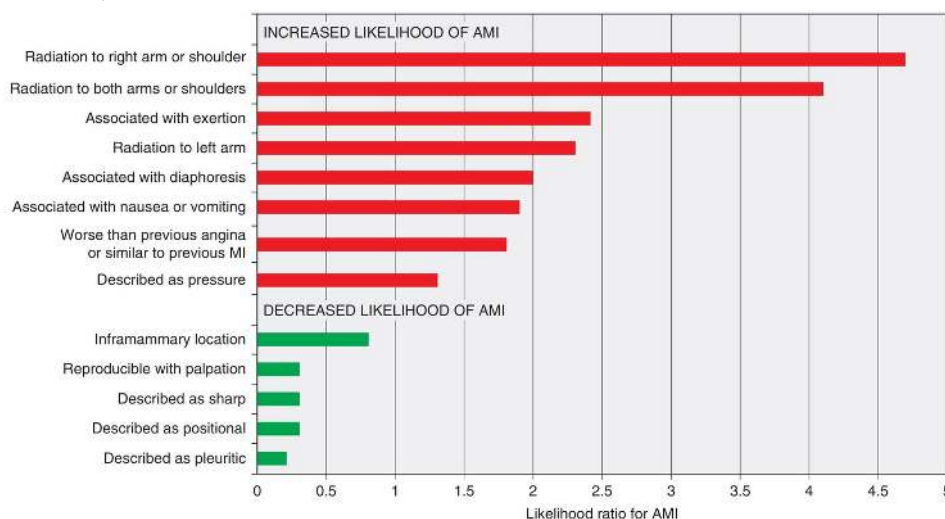
Quality

- Pressure or tightness is typical of ischaemic pain.
- Some patients deny "pain" and instead report dyspnoea or a vague sense of anxiety.
- Asking whether it resembles previous definite ischaemic symptoms is helpful.
- Sharp, knifelike, stabbing or pleuritic pain is unusual for angina. Patients sometimes use "sharp" to convey intensity.
- Pleuritic pain suggests pleural involvement: pericarditis, pulmonary embolism or a parenchymal process.
- "Tearing" or "ripping" pain suggests aortic dissection, although knifelike pain is also common.
- Burning suggests reflux or peptic ulcer, but may occur in ischaemia.
- Oesophageal spasm can mimic angina with severe squeezing pain.

Location and radiation

- Substernal pain radiating to the neck, jaw, shoulder or arms is typical of ischaemia.
- Radiation to **both arms** has a particularly high association with MI.
- Pain demarcated by the tip of one finger is highly unusual for angina.
- Pain only above the mandible or below the epigastrium is rarely angina.
- Retrosternal pain should prompt consideration of oesophageal pain.
- Severe pain radiating to the back, particularly between the shoulder blades, suggests acute aortic syndrome.
- Radiation to the **trapezius ridge** is characteristic of pericardial pain and does not usually occur with angina.

Figure 15-2 — Harrison's 22e, pr.105. **FIGURE 15-2** Association of chest pain characteristics with the probability of acute myocardial infarction (AMI). Note that a subsequent larger study showed a nonsignificant association with radiation to the right arm. (Figure prepared from data in CJ Swap, JT Nagurny: JAMA 294:2623, 2005.)



Pattern

- Ischaemic pain builds over minutes. It is worsened by activity and eased by rest.
- Pain reaching peak intensity immediately suggests aortic dissection, pulmonary embolism or spontaneous pneumothorax.
- Fleeting pain lasting seconds is rarely ischaemic.
- Constant pain lasting hours to days, without ECG change, biomarker rise or clinical sequelae, is unlikely to be ischaemic.

- MI pain is commonly more severe, prolonged (usually ≥ 30 min) and unrelieved by rest.
- Unstable angina is angina occurring at progressively lower exertion or at rest.
- Myocardial injury is irreversible after as little as **20 min** of severe ischaemia.

Provoking and relieving factors

- Ischaemic patients prefer to rest or stop walking. "Warm-up angina" is an exception.
- Pain changing with posture, or with movement of the arms or neck, suggests a musculoskeletal cause.
- Pericarditis pain is worse supine and relieved by sitting up and leaning forward.
- Pain worsened by eating suggests a gastrointestinal cause.
 - Peptic ulcer pain appears 60–90 min after meals.
 - Severe coronary disease can cause postprandial angina.
- Exertion rarely alters gastrointestinal pain.
- Nitroglycerin relief is neither sensitive nor specific for ischaemia, and oesophageal spasm also responds.
- A delay of **>10 min** to nitroglycerin relief suggests a non-ischaemic cause, or severe ischaemia such as acute MI.

Associated symptoms and past history

- Ischaemia may be accompanied by diaphoresis, dyspnoea, nausea, fatigue, faintness and eructations.
- These can occur alone as anginal equivalents, particularly in women, the elderly and diabetics.
- Dyspnoea is not discriminating but suggests a cardiopulmonary cause.
- Sudden respiratory distress should suggest pulmonary embolism or pneumothorax.
- Haemoptysis points to pulmonary embolism or a parenchymal cause.
- Syncope or presyncope suggests haemodynamically significant pulmonary embolism, aortic dissection or ischaemic arrhythmia.
- Nausea and vomiting can occur in MI, more commonly inferior MI (Bezold-Jarisch reflex).
- Past history should cover risk factors for atherosclerosis and venous thromboembolism.
- Connective tissue disease such as Marfan syndrome raises suspicion of aortic syndrome or pneumothorax.
- Aortic dissection is very rare without hypertension or conditions weakening the media (pregnancy, bicuspid aortic valve, Marfan, Ehlers-Danlos).
- Pneumothorax risk factors: male sex, smoking, family history, Marfan syndrome.

Physical examination

- A normal examination is **not** reassuring in unstable ischaemic heart disease.
- General:
 - Anxious, pale, cyanotic or diaphoretic appearance suggests an acute cardiopulmonary disorder.
 - Levine's sign is a clenched fist held against the sternum.
 - Habitus may help: Marfanoid, or a tall thin young man with pneumothorax.
- Vital signs:
 - Aortic emergencies usually present with severe hypertension. Hypotension occurs with coronary compromise or dissection into the pericardium.
 - Sinus tachycardia is important in submassive pulmonary embolism.
 - Tachypnoea and hypoxaemia point to a pulmonary cause.
 - Low-grade fever is non-specific.
- Lungs:
 - Unilateral absent breath sounds suggest pneumothorax.
 - Pulmonary oedema indicates high risk.
- Cardiac:
 - JVP is often normal in ischaemia. It is abnormal in tamponade and acute right ventricular dysfunction.
 - S3 or S4 reflects systolic or diastolic dysfunction.

- Mitral regurgitation or VSD murmurs suggest mechanical complications of STEMI.
- An aortic regurgitation murmur may complicate ascending aortic dissection.
- Aortic stenosis or hypertrophic cardiomyopathy murmurs reveal contributors to ischaemia.
- A pericardial friction rub indicates pericardial inflammation.
- Abdomen: localised tenderness identifies a gastrointestinal cause.

Discriminating features of key causes

Table 2: Features of the major causes of chest discomfort

Cause	Typical features	Clue
Angina / MI	Pressure, substernal, radiates to jaw/arms, builds over minutes	Exertional, relieved by rest; both-arm radiation
Pericarditis	Pleuritic, referred to shoulder/neck	Better sitting forward; trapezius ridge radiation
Aortic dissection	Sudden, severe, tearing; back pain between shoulder blades	Hypertension, Marfan, bicuspid valve
Pulmonary embolism	Sudden pleuritic pain and dyspnoea	Massive PE: substernal pain, syncope, hypotension, right heart failure
Pneumothorax	Sudden onset, mild dyspnoea	Tall thin male, smoker; unilateral absent breath sounds
Pleurisy / pneumonia	Knifelike, worse on inspiration or cough	Fever, parenchymal signs
Reflux / ulcer	Burning, related to meals, posture	Relief with acid-reducing therapy
Chest wall	Reproducible, positional	Costochondritis (Tietze's syndrome) tenderness
Herpes zoster	Dermatomal pain	Rash
Panic disorder	Up to 10% of ED chest pain presentations	Diagnosis of exclusion

- Takotsubo cardiomyopathy mimics MI with abrupt pain, dyspnoea, ST elevation and raised biomarkers.
- It is typically triggered by emotional or physical stress.
- Type 2 MI results from supply–demand imbalance, for example anaemia, hypoxia, hypotension or aortic valve disease. ACS proper is reserved for acute coronary atherothrombosis (type 1 MI).

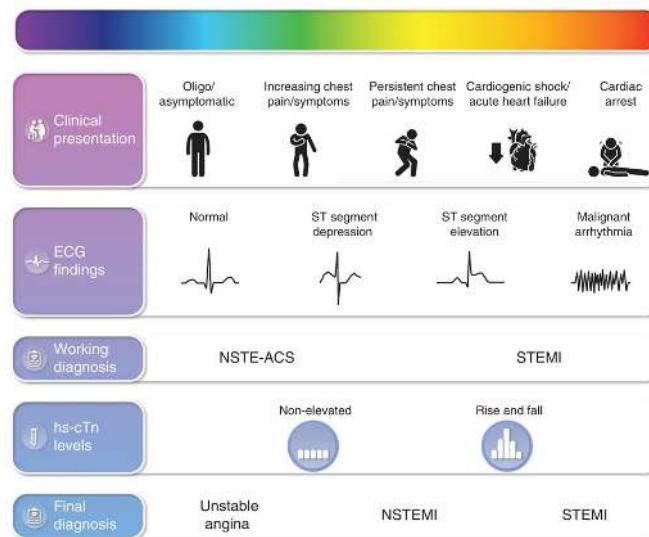
Investigations

- The aim is to select tests guided by the clinical probability of each cause, not to test liberally.

Table 3: Targeted investigations

Test	Finding	Meaning
12-lead ECG, within 10 min of first medical contact	ST elevation	STEMI; go straight to reperfusion pathway
12-lead ECG	ST depression or normal ST	NSTE-ACS or unstable angina, depending on troponin
High-sensitivity cardiac troponin	Rise and fall	Myocardial necrosis: NSTEMI or STEMI
High-sensitivity cardiac troponin	Not elevated	Unstable angina (if ACS suspected)
Stress testing / coronary angiography	Ischaemia, obstructive lesions	Stable IHD diagnosis and risk
CT or CMR angiography	Coronary anatomy	Non-invasive alternative; higher radiation with CT

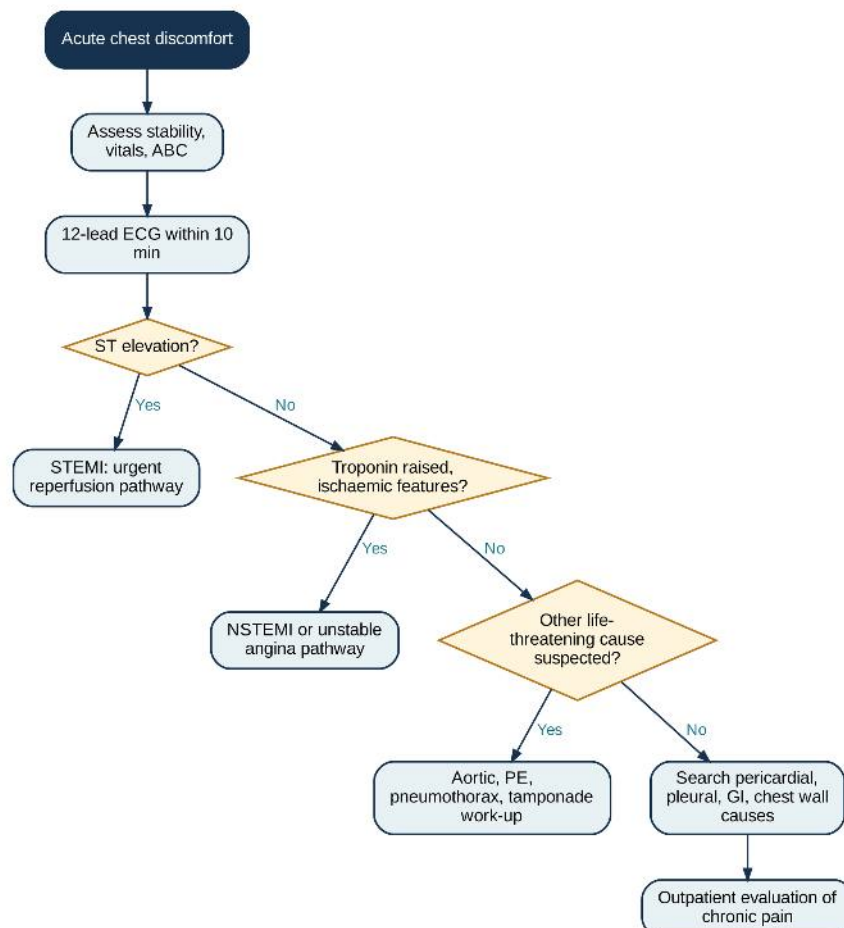
Figure 285-1 — Harrison's 22e, pr.2107. **FIGURE 285-1** Spectrum of acute coronary syndromes. The spectrum of clinical presentations, electrocardiographic findings, and high-sensitivity cardiac troponin levels in patients with acute coronary syndrome. ACS, acute coronary syndrome; ECG, electrocardiogram; hs-cTn, high-sensitivity cardiac troponin; NSTEMI, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarct



- Troponin positivity must be interpreted "in the absence of another explanation". Myocarditis and Takotsubo also raise it.
- Indications for coronary angiography include:
 - Chest pain suggestive of angina with a negative or non-diagnostic stress test
 - Repeated admissions for suspected ACS without a confirmed diagnosis
 - Suspected coronary spasm or a non-atherosclerotic cause

Diagnostic flowchart

Flowchart 1: Approach to acute chest discomfort



Management by cause

GUIDELINE

India: CSI — Position statement for the management of ST elevation myocardial infarction in India — (no year stated in source) · International: ACC/AHA/ACEP/NAEMSP/SCAI — Guideline for the Management of Patients With Acute Coronary Syndromes — 2025. Non-ACS causes of chest pain: Harrison's 22e, ch. 15.

- Suspected STEMI: immediate EMS transport to a PCI-capable hospital, with a first-medical-contact-to-first-device goal of **≤90 minutes** (COR 1, LOE B-NR).
- ACS (unstable angina, NSTEMI, STEMI type 1 MI) is covered by this guideline. Type 2 MI, SCAD and MINOCA are handled elsewhere.
- Stratify NSTEMI-ACS risk with the TIMI score (risk of death, MI or urgent revascularisation at 14 days):
 - 7 markers (1 point each): age ≥65, known CAD ≥50% stenosis, ST deviation ≥0.5 mm, raised markers, ≥2 anginal episodes in 24 h, aspirin use in the past 7 days, ≥3 CAD risk factors.
 - Event rates: 0–1 marker 5%, 2 markers 8%, 3 markers 13%, 4 markers 20%, 5 markers 26%, 6–7 markers 41%.

Table 285-1 — Harrison's 22e, pr.2107. TABLE 285-1 TIMI Risk Score for NSTEMI-ACS

RISK MARKERS	
• Age ≥65 years • Known CAD (≥50% stenosis) • ST deviation >0.5 mm on presenting ECG	• ↑ cardiac markers • ≥2 original episodes in prior 24 h • Prior angina • ≥3 CAD risk factors
NO. OF RISK MARKERS	INCIDENCE OF ADVERSE CARDIAC EVENTS ^a (%)
0/1	5
2	8
3	13
4	20

- Other causes are managed by treating the specific condition identified. The chapters to consult are 281 (pericardium), 290 (pulmonary embolism), 291 (aorta) and 305 (pneumothorax).
- Stable angina plan:
 - Explain the condition and reassure.
 - Treat aggravating conditions.
 - Adapt activity.
 - Treat risk factors.
 - Give drug therapy for angina.
 - Consider revascularisation.

Prognosis and risk markers

- Principal prognostic indicators in IHD:
 - Age
 - LV function
 - Site and severity of coronary narrowing
 - Activity of ischaemia
- Left main stenosis >50%, or proximal LAD disease, carries greater risk.
- Patients with chest pain but normal LV function and normal coronary arteries have an excellent prognosis.

- Even in "low-risk" acute chest pain, the 30-day major cardiovascular event rate was **2.5%** in one large study.

PEARLS

- Quality of pain alone never makes the diagnosis, and severity has poor accuracy.
- Always ask what must not be missed: ACS, aortic dissection, pulmonary embolism, tension pneumothorax and tamponade. Oesophageal rupture is the urgent non-cardiopulmonary cause.
- Obtain an ECG within 10 min of first medical contact in suspected ACS.
- Radiation to both arms is strongly associated with MI.
- Pain peaking instantly suggests dissection, pulmonary embolism or pneumothorax. Ischaemic pain builds over minutes.
- Pain localised to one fingertip, or lasting only seconds, is rarely angina.
- Nitroglycerin response does not separate cardiac from oesophageal pain.
- Women, the elderly and diabetics often present with anginal equivalents.
- A normal examination does not exclude unstable ischaemic heart disease.
- Pericarditis pain is positional, with trapezius ridge radiation. Takotsubo can mimic STEMI.

11. Abdominal pain — mechanisms and differential diagnosis by location

ASKED 1* • Intermediate answer

Asked in: Jun 2022 P-I Q2(b) (4 marks) • Jun 2022 P-I Q2(c) (4 marks)

Q: Discuss the different mechanisms for pain originating in the abdomen. [4]

Q: Write about differential diagnosis of pain abdomen by location. [4]

SOURCE Harrison's 22e — Ch 16 Abdominal Pain, §Some mechanisms of pain originating in the abdomen; Referred pain; Metabolic crises; Immunocompromise; Neurogenic causes; Approach to the patient — pp. 110–112

Definition

- Abdominal pain is a symptom with visceral, parietal (somatic), referred and non-organic origins. Its **location, character and chronological sequence** guide the diagnosis.
- Severity of pain does not necessarily correlate with the severity of the underlying condition. The most obvious "acute abdomen" may not need surgery, while the mildest pain could.
- Harrison's 22e, ch. 16 covers this topic. No guideline-based management applies, so no guideline strip is needed.

Mechanisms of pain originating in the abdomen

Inflammation of the parietal peritoneum

- The pain is **steady and aching**. It lies directly over the inflamed area and is carried by somatic nerves.
- Intensity depends on the type and amount of material and on the rate of exposure.
 - Sterile acidic gastric juice causes more pain than the same amount of contaminated, pH-neutral faeces.
 - Enzymatically active pancreatic juice causes more pain than sterile bile.
 - Blood and urine are bland irritants and may go unnoticed unless the exposure is sudden and massive.
 - Bacterial contamination (PID, distal bowel perforation) gives low-intensity pain until mediators accumulate.
- The pain is accentuated by palpation, coughing, sneezing or movement. The patient with peritonitis **lies still**, whereas the patient with colic thrashes about.
- **Tonic reflex spasm** of the abdominal muscles is localised to the involved segment.
 - It may be minimal in a retrocecal appendix or a perforation into the lesser sac.
 - It may be absent in obtunded, debilitated, immunosuppressed or psychotic patients, and in slowly evolving processes.

Obstruction of hollow viscera

- Intraluminal obstruction gives **intermittent, colicky pain** that is less well localised than peritoneal pain. Distension can also give steady pain with rare paroxysms.
- Small bowel: poorly localised periumbilical or supraumbilical colic. With strangulation, pain may spread to the lower lumbar region from traction on the mesenteric root.
- Colon: less intense, infraumbilical pain that may radiate to the lumbar region.
- Biliary tree:
 - Sudden distension gives **steady** pain, so "biliary colic" is a misnomer.
 - The gallbladder causes RUQ pain radiating to the right posterior thorax or the tip of the right scapula.
 - The common bile duct causes epigastric pain that may radiate to the upper lumbar region.
 - Gradual dilatation (e.g., carcinoma of the pancreatic head) may be painless or cause only mild aching.
- Pancreatic duct: the pain is like that of the CBD but is worse on recumbency and relieved by sitting upright.
- Urinary tract:
 - Bladder: dull suprapubic pain, or only restlessness in an obtunded patient.
 - Intravesical ureter: severe suprapubic and flank pain radiating to the penis, scrotum or inner thigh.
 - Ureteropelvic junction: pain near the costovertebral angle.
 - Rest of the ureter: flank pain extending into the same side of the abdomen.

Vascular disturbances

- Pain is not always sudden and catastrophic.
- Superior mesenteric artery occlusion may give only mild, diffuse pain for 2–3 days before collapse. This early pain is due to hyperperistalsis.
- **Pain out of proportion to physical findings**, without tenderness or rigidity, is characteristic of SMA occlusion.
- Pain radiating to the sacrum, flank or genitalia signals a possible rupturing aortic aneurysm. It may persist for days before rupture.

Abdominal wall

- The pain is constant and aching. It is worsened by movement, prolonged standing and pressure.
- Rectus sheath haematoma, now mostly with anticoagulants, may present as a lower-quadrant mass.
- Involvement of muscles elsewhere in the body points to myositis rather than another cause.

Distension of visceral surfaces

- Examples are haemorrhage into the hepatic or renal capsule, and mesenteric traction.

Table 1: Mechanism, character and clue

Mechanism	Character	Discriminating clue
Parietal peritoneal inflammation	Steady, aching, localised	Lies still; guarding; worse on cough
Hollow viscus obstruction	Colicky, poorly localised	Restless, thrashing
Biliary distension	Steady, RUQ or epigastric	Tip of scapula radiation
Pancreatic duct	Epigastric, boring	Worse supine, better upright
Mesenteric ischaemia	Diffuse, continuous	Pain out of proportion to signs
Abdominal wall	Constant, aching	Worse on movement and pressure

Table 16-2 — Harrison's 22e, pr.110. TABLE 16-2 Some Important Causes of Abdominal Pain

Pain Originating in the Abdomen	
Parietal peritoneal inflammation	Vascular disturbances
Bacterial contamination	Embolism or thrombosis
Perforated appendix or other	Vascular rupture

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B:

Referred and other non-visceral pain

- **Intrathoracic disease** must be considered in every patient with abdominal pain, especially upper abdominal pain.
 - Common masqueraders are myocardial or pulmonary infarction, pneumonia, pericarditis and oesophageal disease.
 - Diaphragmatic pleuritis gives RUQ and supraclavicular pain, which differs from the subscapular pain of biliary distension.
- Features favouring thoracic origin:
 - Splinting of the hemithorax with respiratory lag.
 - Muscle spasm that diminishes on inspiration, whereas abdominal spasm persists in both phases.
 - Palpation does not accentuate the pain and may relieve it.
- Spinal root pain is worsened by cough, sneeze or strain, with dermatomal hyperaesthesia.
- Testicular or seminal vesicle pain is dull and poorly localised, and worse with pressure on those organs.
- Metabolic causes:
 - Hyperlipidaemia (via pancreatitis), C1 esterase deficiency, familial Mediterranean fever and COVID-19 (rarely).
 - Porphyria and lead colic mimic obstruction because of hyperperistalsis.
 - Uraemia and diabetes give shifting, nonspecific pain.
 - In DKA, pain that does not resolve with metabolic correction suggests an organic cause.
 - Black widow bite causes abdominal and back muscle rigidity.
- Neurogenic:
 - Causalgia is burning, in a peripheral nerve distribution, with no rigidity and no relation to food.
 - Root pain is lancinating (e.g., herpes zoster, tabes, diabetes).
- Functional pain (IBS) fits none of these patterns. It has altered bowel habit, stress precipitation, rare vomiting and inconsistent tenderness.
- Immunocompromised patients have masked signs.
 - CMV, mycobacteria, protozoa and fungi can cause pain.
 - Neutropenic enterocolitis (typhlitis) occurs after chemotherapy.

Differential diagnosis by location

- Location helps narrow the differential, but the **chronological sequence** of events is often more important.

Table 2: Differential diagnosis of abdominal pain by usual location

Site	Causes
Right upper quadrant	Cholecystitis, cholangitis, pancreatitis, pneumonia/empyema, pleurisy, subdiaphragmatic abscess, hepatitis, Budd-Chiari
Epigastric	Peptic ulcer, gastritis, GERD, pancreatitis, MI, pericarditis, ruptured aortic aneurysm, oesophagitis
Left upper quadrant	Splenic infarct, rupture or abscess, gastritis, gastric ulcer, pancreatitis, subdiaphragmatic abscess
Right lower quadrant	Appendicitis, salpingitis, inguinal hernia, ectopic pregnancy, nephrolithiasis, IBD, mesenteric lymphadenitis, typhlitis
Periumbilical	Early appendicitis, gastroenteritis, bowel obstruction, ruptured aortic aneurysm
Left lower quadrant	Diverticulitis, salpingitis, inguinal hernia, ectopic pregnancy, nephrolithiasis, IBS, IBD
Diffuse	Gastroenteritis, mesenteric ischaemia, obstruction, IBS, peritonitis, diabetes, malaria, FMF, metabolic or psychiatric disease

Table 16-3 — Harrison's 22e, pr.112. TABLE 16-3 Differential Diagnoses of Abdominal Pain by Usual Location

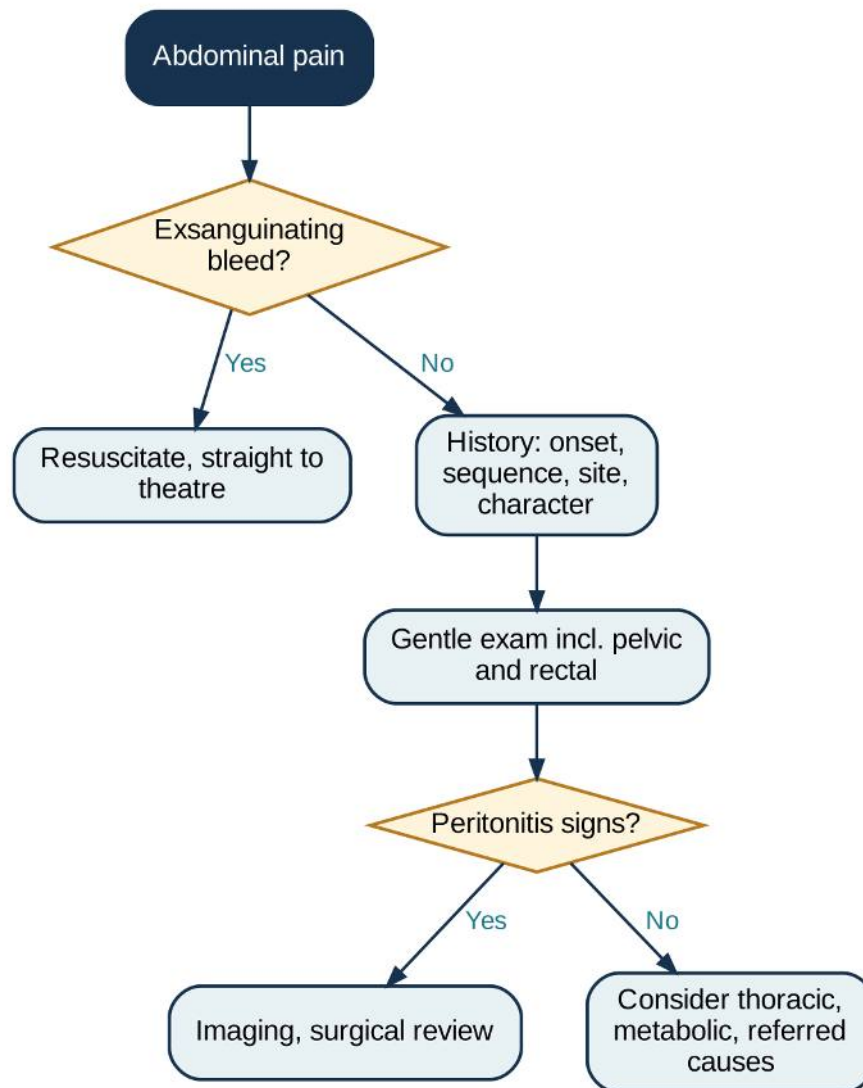
Right Upper Quadrant	Epigastric	Left Upper Quadrant
Cholecystitis	Peptic ulcer disease	Splenic infarct
Cholangitis	Gastritis	Splenic rupture
Pancreatitis	GERD	Splenic abscess
Pneumonia/empyema	Pancreatitis	Gastritis
Pleurisy/pleurodynia	Myocardial infarction	Gastric ulcer
Subdiaphragmatic abscess	Pericarditis	Pancreatitis
Hepatitis	Ruptured aortic aneurysm	Subdiaphragmatic abscess
Budd-Chiari syndrome	Esophagitis	
Right Lower Quadrant	Periumbilical	Left Lower Quadrant
Appendicitis	Early appendicitis	Diverticulitis
Salpingitis	Gastroenteritis	Salpingitis
Inguinal hernia	Bowel obstruction	Inguinal hernia
Ectopic pregnancy	Ruptured aortic aneurysm	Ectopic pregnancy
Nephrolithiasis		Nephrolithiasis
Inflammatory bowel disease		Irritable bowel syndrome
Mesenteric lymphadenitis		Inflammatory bowel disease
Typhlitis		
Diffuse Nonlocalized Pain		
Gastroenteritis	Malaria	
Mesenteric ischemia	Familial	
Bowel obstruction	Mediterranean fever	
Irritable bowel syndrome	Metabolic diseases	
Peritonitis	Psychiatric disease	
Diabetes		

Abbreviation: GERD, gastroesophageal reflux disease.

Approach to the patient

- Only patients with exsanguinating haemorrhage (ruptured aneurysm) go straight to theatre. They need venous access and no unnecessary imaging.
- A detailed history facilitates decisions and gives a reasonably accurate diagnosis before further testing.
- Take a menstrual history. A gravid uterus alters anatomy, and leukocytosis may be physiological in pregnancy.
- Do not withhold analgesics until a diagnosis is made.
- Examine gently. Use gentle percussion or ask the patient to cough, instead of eliciting sudden-release rebound.
- Pelvic and rectal examination is mandatory, because signs may be absent in pelvic peritonitis.
- Bowel sounds are one of the least revealing findings. A truly silent abdomen suggests sudden-onset chemical peritonitis.
- Laboratory tests rarely establish a diagnosis. Leukocytosis alone should never decide on surgery. WBC >20,000/ μ L may occur with perforation, but also with pancreatitis, cholecystitis, PID and infarction.

Flowchart 1: Approach to acute abdominal pain

**PEARLS**

- Peritonitis: patient lies still. Colic: patient thrashes.
- "Biliary colic" is steady pain, not truly colicky.
- Pain out of proportion to findings suggests SMA occlusion.
- Pain to the sacrum, flank or genitalia suggests a rupturing aortic aneurysm.
- Always exclude intrathoracic disease in upper abdominal pain.
- Referred pain: spasm decreases on inspiration and palpation does not worsen it.
- Pelvic and rectal examinations are mandatory in every patient with abdominal pain.
- Leukocytosis alone never decides on operation.
- Consider metabolic causes (DKA, porphyria, lead, FMF) when the cause is obscure.

12. Headache — pathophysiology, ICHD-3 classification and approach to new-onset headache

ASKED 3* · Long answer

Asked in: Jun 2022 P-II Q8(a) (4 marks) · May 2024 P-I Q5(a) (5 marks) · Dec 2025 P-III Q5(a) (2 marks) · Dec 2025 P-III Q5(b) (3 marks) · Dec 2025 P-III Q5(c) (5 marks)

Q: Discuss the pathophysiology of headache. [4]

Q: Classify primary headache disorders. [5]

Q: Enumerate the ICHD-3 classification of headache disorders. [2]

Q: Outline a systematic diagnostic approach to a patient with new-onset headache. [3]

Q: Describe the red-flag features and initial investigations for secondary headache. [5]

SOURCE Harrison's 22e — Ch 17 Headache, §General principles to Primary care and headache management — pp. 113–115, 117
Harrison's 22e — Ch 441 Migraine and Other Primary Headache Disorders, Table 441-1 and §Treatment — pp. 3463, 3474
[W1] International Headache Society — The International Classification of Headache Disorders, 3rd edition (ICHD-3) — 2018 — <https://ichd-3.org/wp-content/uploads/2018/01/The-International-Classification-of-Headache-Disorders-3rd-Edition-2018.pdf> (the AHS 2024 CGRP statement is summarised from the guideline pack, <https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14692>)

Definition and importance

- **Headache** is pain felt in the head. It causes more disability globally than any other neurologic problem.
- The **International Headache Society (IHS)** classification divides headaches into **primary** and **secondary**.
 - **Primary:** the headache and its associated features form the disorder itself.
 - **Secondary:** the headache is caused by an exogenous disorder.
- Mild secondary headache (e.g. with an upper respiratory infection) is common but rarely worrisome.
- Life-threatening headache is uncommon, but vigilance is needed to recognise it.
- **Relative frequency**
 - Primary headache is mostly **tension-type (69%)**, then **migraine (16%)**. Cluster headache is about **0.1%**.
 - Secondary headache is mostly **systemic infection (63%)**, then head injury (4%) and vascular disorders (1%).
 - Subarachnoid haemorrhage is <1% and brain tumour about 0.1%.
- >90% of patients presenting to primary care with headache have **migraine**.

Table 17-1 — Harrison's 22e, pr.113. **TABLE 17-1 Common Causes of Headache**

TABLE 17-1 Common Causes of Headache			
PRIMARY HEADACHE		SECONDARY HEADACHE	
TYPE	%	TYPE	%
Tension-type	69	Systemic infection	63
Migraine	16	Head injury	4
Idiopathic stabbing	2	Vascular disorders	1
Exertional	1	Subarachnoid hemorrhage	<1
Cluster	0.1	Brain tumor	0.1

Source: After J Olesen et al: *The Headaches*. Philadelphia, Lippincott Williams & Wilkins, 2005.

Pathophysiology of headache

Pain-producing structures

- Pain usually arises when peripheral nociceptors respond to tissue injury, visceral distension or other stimuli. This is a normal physiological response.
- Pain can also arise when pain pathways in the peripheral or central nervous system are damaged or inappropriately activated. Headache may arise from either or both mechanisms.
- Few cranial structures are pain-producing.
 - Pain-producing: the **scalp, meningeal arteries, dural sinuses, falx cerebri and proximal segments of the large pial arteries**.

- Not pain-producing; the **ventricular ependyma, choroid plexus, pial veins and much of the brain parenchyma**.

Key structures in primary headache

- The large intracranial vessels, the dura mater and the peripheral terminals of the **trigeminal nerve** that innervate them.
- The **caudal trigeminal nucleus**, which extends into the dorsal horn of the upper cervical cord and receives C1–C2 root input. This is the **trigeminocervical complex**.
- Rostral pain-processing regions: the **ventroposteromedial thalamus** and the cortex.
- **Pain-modulatory systems** (hypothalamus and brainstem) that modulate trigeminal nociceptive input at all levels. They also influence vegetative functions.

Trigeminovascular system and autonomic features

- Trigeminal innervation of the large intracranial vessels and dura is the **trigeminovascular system**.
- **Cranial autonomic symptoms** are lacrimation, conjunctival injection, nasal congestion, rhinorrhoea, periorbital swelling, aural fullness and ptosis.
 - They are prominent in the **trigeminal autonomic cephalalgias (TACs)**, such as cluster headache and paroxysmal hemicrania.
 - They are often seen in migraine, even in children.
- They reflect activation of **cranial parasympathetic pathways**. Any vascular change in migraine or cluster headache is driven by these autonomic systems.
- These changes are **secondary, not causative**, events in the headache cascade.
- Cranial autonomic symptoms can be mistaken for sinus inflammation. This leads to overdiagnosis and inappropriate management.
- Migraine and other primary headaches are **not "vascular headaches"**. Vascular changes are not reliable, and treatment outcomes cannot be predicted from vascular effects.
- **Migraine is a brain disorder** and should be managed as such.

Classification of headache (ICHD-3)

- The **ICHD-3 (IHS, 2018)** has four parts:
 - Part One: the primary headaches.
 - Part Two: the secondary headaches.
 - Part Three: painful cranial neuropathies, other facial pain and other headaches.
 - Part Four: the appendix.
- Almost every ICHD-3 diagnosis ends with the criterion "not better accounted for by another ICHD-3 diagnosis".

Table 1: ICHD-3 structure (chapters 1–14)

Part	Chapters	Content
One: Primary	1 Migraine; 2 Tension-type headache; 3 Trigeminal autonomic cephalalgias; 4 Other primary headache disorders	No other causative disorder
Two: Secondary	5 Trauma or injury to head/neck; 6 Cranial or cervical vascular disorder; 7 Non-vascular intracranial disorder; 8 Substance or its withdrawal; 9 Infection; 10 Disorder of homeostasis; 11 Cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial/cervical structure; 12 Psychiatric disorder	Headache attributed to another disorder
Three	13 Painful lesions of cranial nerves and other facial pain; 14 Other headache disorders	Neuralgias, facial pain and unclassified headache

Classification of primary headache disorders

Table 441-1 — Harrison's 22e, pr.3463. **TABLE 441-1 Primary Headache Disorders, Modified from International Classification of Headache Disorders-III (Headache Classification Committee of the International Headache Society, 2018)**

1. Migraine	1.1 Migraine without aura 1.2 Migraine with aura 1.2.1 Migraine with typical aura 1.2.1.1 Typical aura with headache 1.2.1.2 Typical aura without headache 1.2.2 Migraine with brainstem aura 1.2.3 Hemiplegic migraine 1.2.3.1 Familial hemiplegic migraine (FHM) 1.2.3.1.1 Familial hemiplegic migraine type 1 1.2.3.1.2 Familial hemiplegic migraine type 2 1.2.3.1.3 Familial hemiplegic migraine type 3 1.2.3.1.4 Familial hemiplegic migraine, other loci 1.2.3.2 Sporadic hemiplegic migraine 1.2.4 Retinal migraine 1.3 Chronic migraine 1.4 Complications of migraine 1.4.1 Status migrainosus 1.4.2 Persistent aura without infarction 1.4.3 Migrainous infarction 1.4.4 Migraine aura-triggered seizure 1.5 Probable migraine 1.5.1 Probable migraine without aura 1.5.2 Probable migraine with aura 1.6 Episodic syndromes that may be associated with migraine 1.6.1 Recurrent gastrointestinal disturbance 1.6.1.1 Cyclical vomiting syndrome 1.6.1.2 Abdominal migraine 1.6.2 Benign paroxysmal vertigo 1.6.3 Benign paroxysmal torticollis A 1.6.4 Infantile colic A 1.6.6 Vestibular migraine
2. Tension-type headache	2.1 Infrequent episodic tension-type headache 2.2 Frequent episodic tension-type headache 2.3 Chronic tension-type headache 2.4 Probable tension-type headache
3. Trigeminal autonomic cephalalgias	3.1 Cluster headache 3.1.1 Episodic cluster headache 3.1.2 Chronic cluster headache 3.2 Paroxysmal hemicrania 3.2.1 Episodic paroxysmal hemicrania 3.2.2 Chronic paroxysmal hemicrania 3.3 Short-lasting unilateral neuralgiform headache attacks 3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) 3.3.1.1 Episodic SUNCT 3.3.1.2 Chronic SUNCT 3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) 3.3.2.1 Episodic SUNA 3.3.2.2 Chronic SUNA 3.4 Hemicrania continua 3.5 Probable trigeminal autonomic cephalalgia
4. Other primary headache disorders	4.1 Primary cough headache 4.2 Primary exercise headache 4.3 Primary headache associated with sexual activity 4.4 Primary thunderclap headache 4.5 Cold-stimulus headache 4.5.1 Headache attributed to external application of a cold stimulus 4.5.2 Headache attributed to ingestion or inhalation of a cold stimulus 4.6 External-pressure headache 4.6.1 External-compression headache 4.6.2 External-traction headache 4.7 Primary stabbing headache 4.8 Nummular headache 4.9 Hypnic headache 4.10 New daily persistent headache (NDPH)

• 1. Migraine

- 1.1 Migraine without aura.
- 1.2 Migraine with aura:
 - 1.2.1 typical aura (with or without headache)
 - 1.2.2 brainstem aura
 - 1.2.3 hemiplegic migraine (familial types 1–3 and other loci; sporadic)
 - 1.2.4 retinal migraine
- 1.3 Chronic migraine.
- 1.4 Complications: status migrainosus, persistent aura without infarction, migrainous infarction, aura-triggered seizure.

- 1.5 Probable migraine.
- 1.6 Episodic syndromes that may be associated with migraine: cyclical vomiting, abdominal migraine, benign paroxysmal vertigo, benign paroxysmal torticollis.
- **2. Tension-type headache (TTH)**
 - 2.1 Infrequent episodic.
 - 2.2 Frequent episodic.
 - 2.3 Chronic.
 - 2.4 Probable.
- **3. Trigeminal autonomic cephalalgias**
 - 3.1 Cluster headache (episodic or chronic).
 - 3.2 Paroxysmal hemicrania (episodic or chronic).
 - 3.3 Short-lasting unilateral neuralgiform headache attacks: **SUNCT** (conjunctival injection and tearing) and **SUNA** (cranial autonomic symptoms).
 - 3.4 Hemicrania continua.
 - 3.5 Probable TAC.
- **4. Other primary headache disorders**
 - 4.1 Primary cough headache.
 - 4.2 Primary exercise headache.
 - 4.3 Headache associated with sexual activity.
 - 4.4 Primary thunderclap headache.
 - 4.5 Cold-stimulus headache.
 - 4.6 External-pressure headache.
 - 4.7 Primary stabbing headache.
 - 4.8 Nummular headache.
 - 4.9 Hypnic headache.
 - 4.10 New daily persistent headache (NDPH).
- ICHD-3 introduced new migraine-with-aura criteria that better separate it from TIA. It also moved **chronic migraine** into the main body of the classification.

Chronic daily headache (≥15 days/month)

- Chronic daily headache is **not a single diagnosis**. It is a descriptive term for headache on **≥15 days per month**.
- About **4%** of adults have daily or near-daily headache.
- **Primary causes lasting >4 h/day**: chronic migraine, chronic TTH, hemicrania continua, NDPH and medication-overuse headache.
- **Primary causes lasting <4 h/day**: chronic cluster headache, chronic paroxysmal hemicrania, SUNCT/SUNA and hypnic headache.
- **Secondary causes**: post-traumatic headache, inflammatory causes (giant cell arteritis, sarcoidosis, Behçet's syndrome) and chronic CNS infection.

Table 17-3 — Harrison's 22e, pr.115. TABLE 17-3 Classification of Daily or Near-Daily Headache

Primary		
>4 H DAILY	<4 H DAILY	SECONDARY
Chronic migraine ^a	Chronic cluster headache ^b	Posttraumatic Head injury Iatrogenic Postinfectious
Chronic tension-type headache ^a	Chronic paroxysmal hemicrania	Inflammatory, such as Giant cell arteritis Sarcoidosis Behçet's syndrome
Hemicrania continua ^a	SUNCT/SUNA	Chronic CNS infection
New daily persistent headache ^a	Hypnic headache	Medication-overuse headache ^a

^aMay be complicated by medication overuse. ^bSome patients may have headache >4 h/d.

Abbreviations: CNS, central nervous system; SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

Approach to new-onset headache

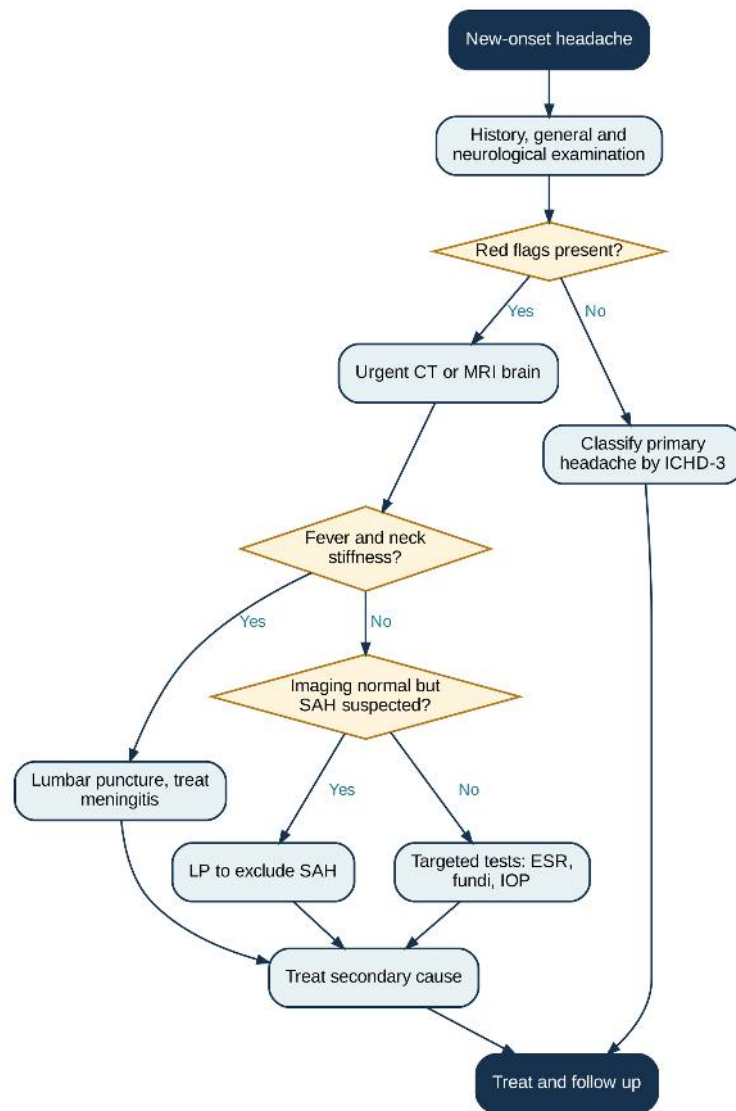
Principles

- The differential diagnosis of a **new, severe headache** differs from that of recurrent headache over many years.
- In new-onset severe headache, the chance of a serious cause is considerably greater. Patients need prompt evaluation.
- Serious causes to consider: **meningitis, subarachnoid haemorrhage, epidural or subdural haematoma, glaucoma, tumour and purulent sinusitis.**
- Most patients with severe headache still have a benign cause, usually **migraine**.

History and examination

- Look for the red flags in Table 2 below.
- Perform a **careful neurological examination**. This is an essential part of the first-step evaluation.
- General evaluation may include:
 - palpation of the cranial arteries
 - passive neck movement and cervical imaging
 - blood pressure and urine examination (cardiovascular and renal status)
 - fundoscopy, intraocular pressure and refraction
- Assess the **psychological state** to identify comorbid depression or anxiety. Mood change seldom explains troublesome headache by itself.

Flowchart 1: Diagnostic approach to new-onset headache



Red-flag features suggesting secondary headache

Table 2: Red flags for a serious underlying disorder

Red flag	Example concern
Sudden-onset headache	Subarachnoid haemorrhage
First severe headache; "worst" headache ever	Intracranial haemorrhage, meningitis
Vomiting that precedes headache	Posterior fossa tumour
Subacute worsening over days or weeks	Mass lesion
Pain induced by bending, lifting or cough	Posterior fossa mass, Chiari malformation, low CSF volume
Pain that disturbs sleep or is present on awakening	Raised intracranial pressure
Known systemic illness	Infection, malignancy
Onset after age 55	Giant cell arteritis, tumour
Fever or unexplained systemic signs	Meningitis, systemic infection
Abnormal neurological examination	Structural lesion
Local tenderness (e.g. temporal artery region)	Temporal arteritis

Table 17-2 — Harrison's 22e, pr.114. TABLE 17-2 Headache Symptoms That Suggest a Serious Underlying Disorder

TABLE 17-2 Headache Symptoms That Suggest a Serious Underlying Disorder

Sudden-onset headache
 First severe headache
 Vomiting that precedes headache
 Subacute worsening over days or weeks
 Pain induced by bending, lifting, cough
 Pain that disturbs sleep or presents immediately upon awakening
 Known systemic illness
 "Worst" headache ever
 Onset after age 55
 Fever or unexplained systemic signs
 Abnormal neurologic examination
 Pain associated with local tenderness, e.g., region of temporal artery

Specific serious secondary causes: clues and initial tests

Table 3: Clues and first-line investigation by cause

Cause	Clinical clue	Initial investigation
Meningitis	Acute severe headache with stiff neck and fever; pain worse on eye movement	LP is mandatory
Subarachnoid haemorrhage	Maximal in <5 min, severe, lasting >5 min, stiff neck, no fever	CT head; LP if CT is normal, since a small bleed can be missed
Brain tumour	Dull deep ache worse on exertion; vomiting before headache in posterior fossa tumours	CT or MRI
Giant cell arteritis	Age ≥50, scalp tenderness, jaw claudication, polymyalgia rheumatica, fever	ESR (can be normal); temporal artery biopsy
Glaucoma	Prostrating headache with nausea and vomiting, red eye, fixed mid-dilated pupil	Intraocular pressure measurement
Raised CSF pressure (e.g. idiopathic intracranial hypertension)	Headache on waking, worse lying down, transient visual obscurations	MRI with MR venogram, then LP with opening pressure

- **Thunderclap onset:** investigate with neuroimaging (CT or MRI with MR angiography) and **CSF examination**.
 - The differential includes sentinel aneurysmal bleed, RCVS, arterial dissection and cerebral venous thrombosis.
 - With posterior leukoencephalopathy, consider PRES and cerebral angiitis.
- **Other tests:** blood pressure and urine examination (cardiovascular and renal status), and funduscopy and refraction for the eyes.

Initial investigations: summary

- **Neuroimaging** is indicated in patients with an abnormal examination or recent-onset headache.
 - **CT or MRI** brain. For initial screening of intracranial pathology they appear equally sensitive.
- **LP** is required in some circumstances, unless a benign cause can otherwise be established.
 - Examples: suspected meningitis, or suspected SAH with a normal CT.
- **ESR** when giant cell arteritis is suspected, with temporal artery biopsy. Start prednisone **80 mg daily for the first 4–6 weeks** when clinical suspicion is high.
 - A normal ESR does not exclude giant cell arteritis.
- Headache in the setting of known malignancy suggests metastases or carcinomatous meningitis.
- Management of secondary headache focuses on **diagnosing and treating the underlying condition**.

Management principles

GUIDELINE

Harrison's 22e, ch. 17 and ch. 441 • International: IHS — ICHD-3 — 2018

- **Secondary headache:** treat the underlying cause.
- **Chronic daily headache:** first diagnose and treat any secondary headache.
 - **Preventives** for migraine or TTH-type CDH are amitriptyline or nortriptyline up to 1 mg/kg, started at 10–25 mg daily and given about 12 h before expected waking.
 - Other options for migraine: topiramate, valproate, propranolol, flunarizine, candesartan, CGRP monoclonal antibodies and gepants.
- **Medication-overuse headache:** reduce the drug by **10% every 1–2 weeks**, or stop abruptly if no contraindication. Use a headache diary and naproxen 500 mg bid as a bridge.
- **Low CSF volume headache:** bed rest, then **IV caffeine 500 mg in 500 mL saline over 2 h** after an ECG. A blood patch is usually curative if a leak is found.
- **Idiopathic intracranial hypertension:** acetazolamide 250–500 mg bid and weight loss. If that fails, use topiramate.
- **Primary care**
 - Identify the few worrisome secondary headaches among the many benign ones.
 - Refer patients with no clear diagnosis, a primary headache other than migraine or TTH, or failure of two or more standard therapies.
- **Migraine prevention:** the AHS (2024) made CGRP-targeting therapies first-line. This removed the earlier requirement to try two non-specific oral preventives first.

PEARLS

- Pain-sensitive structures: scalp, meningeal arteries, dural sinuses, falx cerebri and proximal pial arteries. The brain parenchyma, choroid plexus and ependyma are pain-insensitive.
- The **trigemino-cervical complex** (caudal trigeminal nucleus plus C1–C2 input) is the key relay in primary headache.
- Cranial autonomic features are secondary events driven by parasympathetic activation. They do not mean sinusitis, and migraine is not a "vascular headache".
- ICHD-3 has 14 chapters: 1–4 primary, 5–12 secondary, 13–14 neuropathies and other headaches.
- Primary headache chapters: migraine, TTH, TACs and other primary headaches.
- Red flags to remember: sudden onset, first or worst headache, onset after 55, fever, abnormal examination, pain on cough or bending, and vomiting before headache.
- CT and MRI are equally sensitive for initial screening. A normal CT does not exclude SAH, so do an LP.
- A normal ESR does not exclude giant cell arteritis. Start prednisone 80 mg daily without waiting for biopsy if suspicion is high.
- Chronic daily headache means ≥ 15 days a month, and medication overuse is a common complication.

13. Pathogenesis of fever, fever with rash and approach to FUO

ASKED 1* • Long answer

Asked in: Jun 2022 P-I Q3(a) (3 marks) • Jun 2022 P-I Q3(b) (2 marks) • Jun 2022 P-I Q3(c) (5 marks)

Q: Discuss the pathogenesis of fever. [3]

Q: Enumerate the causes of fever with skin eruptions. [2]

Q: Draw an algorithm for approach to a patient with fever of unknown origin. [5]

SOURCE Harrison's 22e — Ch 21 Fever and Rash, §Approach and Classification — pp. 137, 139, 141

Harrison's 22e — Ch 22 Fever of Unknown Origin, §Definition to Treatment — pp. 149, 151, 153, 154

[W1] PMC — Pathogenesis of Fever — <https://pmc.ncbi.nlm.nih.gov/articles/PMC7122269/>

[W2] PMC (Front Neurosci) — Neural Mechanisms of Inflammation-Induced Fever — <https://pmc.ncbi.nlm.nih.gov/articles/PMC6047205/>

NOT IN TEXTBOOK

Searched in the textbook pages supplied: "pathogenesis of fever", "pyrogen", "hypothalamic set point", "endogenous pyrogen" (Ch 18 Fever). That part is not covered, so the pathogenesis section below is taken from peer-reviewed reviews. Fever with rash (Ch 21) and FUO (Ch 22) come from Harrison's 22e.

Definition and scope

- This answer covers three linked parts: the **pathogenesis of fever**, the **causes of fever with skin eruption**, and an **algorithm for FUO**.
- Fever is a regulated rise of the hypothalamic set point. It is not the same as hyperthermia, where the set point is unchanged.
- Hyperpyrexia needs active cooling. Cooling blankets help lower temperature, but they should not be used without oral antipyretics.
- In hyperpyretic patients with CNS disease or trauma, lowering core temperature reduces the harmful effects of heat on the brain.
- FUO is a **prolonged** febrile illness with no cause after a defined work-up.

Pathogenesis of fever (3 marks)

- **Step 1: exogenous pyrogens.** These are microorganisms or their products (toxins). Exogenous pyrogens make host cells, mainly macrophages, release endogenous pyrogens.
- **Step 2: endogenous pyrogens.** These are cytokines (IL-1, TNF, IL-6 and interferons) released into the bloodstream.
- **Step 3: signalling to the brain.** Proinflammatory cytokines bind receptors on brain endothelial cells. This drives prostaglandin E_2 synthesis in those cells.
- **Step 4: hypothalamus.** Endogenous pyrogens reach the OVLT of the hypothalamic thermoregulatory centre. There they induce prostaglandins, of which PGE_2 is the most important.
- **Step 5: receptor and set point.** PGE_2 binds its EP3 receptor in the preoptic hypothalamus and starts thermogenesis. This raises the thermostatic set point.
- **Step 6: effector response.** PGE_2 binding disinhibits presympathetic neurons in the brainstem. Heat production rises and heat loss falls until body temperature reaches the new set point.
- Clinically, the set-point rise causes chills and rigors, and vasoconstriction (cold peripheries) until the new set point is reached.
- **Fever versus hyperthermia.** Fever does not climb relentlessly because the hypothalamic centre keeps it under control. In hyperthermia the set point is unchanged.
- **Non-infective causes.** Infection is the commonest cause of fever, but it also occurs in hypersensitivity, autoimmune disease and malignancy.
- **Protective role.** Cytokines activate B and T lymphocytes. Fever arises together with lymphocyte activation, which supports a protective role for fever.
- Fever can aggravate pre-existing cardiac, pulmonary or CNS impairment.
- Children with a seizure history need aggressive fever reduction. However, there is no correlation between absolute temperature and the onset of febrile seizure.

Approach to fever with rash: history and examination

- A rash with fever can allow prompt diagnosis, life-saving therapy or infection-control action.
- **History to elicit:**
 - immune status
 - drugs in the previous month
 - travel
 - immunisation
 - animal and arthropod exposure

- dietary exposure
- cardiac disease or prosthetic material
- ill contacts
- sexual exposure
- Record the **site of onset of the rash and its direction and rate of spread.**
- **Identify the lesion type:**
 - Macule: flat, with changed colour.
 - Papule: raised, <5 mm.
 - Plaque: >5 mm and flat-topped.
 - Nodule: >5 mm and rounded.
- **Fluid and vascular lesions:**
 - Vesicle <5 mm; bulla >5 mm.
 - Petechiae: non-palpable purpura <3 mm; ecchymoses >3 mm.
 - Palpable purpura means vasculitis.
 - An eschar (tâche noire) is a necrotic lesion with a black crust.
- Also note configuration (annular or target) and distribution (central or peripheral).
- Morphology evolves. For example, the rash of Rocky Mountain spotted fever may begin as blanchable macules, and sometimes no rash appears at all.

Causes of fever with skin eruption (2 marks)

- The classification is by type of eruption. The categories are:
 - centrally distributed maculopapular
 - peripheral
 - confluent desquamative erythematous
 - vesiculobullous
 - urticaria-like
 - nodular
 - purpuric
 - ulcerated
 - with eschars

Table 21-1 — Harrison's 22e, pr.139. TABLE 21-1 Diseases Associated with Fever and Rash

DISEASE	ETIOLOGY	DESCRIPTION
Rickettsial spotted fevers (Fig. 21-8)	<i>Rickettsia conorii</i> (boutonneuse fever), <i>Rickettsia australis</i> (North Queensland tick typhus), <i>Rickettsia sibirica</i> (Siberian tick typhus), <i>Rickettsia africae</i> (African tick-bite fever), and others	Eschar common at bite site (rarely, vesicular and petech on proximal extremities, sp and face)
Human monocytotropic ehrlichiosis ⁴	<i>Ehrlichia chaffeensis</i>	Maculopapular eruption (40% involves trunk and extremities); petechial
Leptospirosis	<i>Leptospira interrogans</i> and other <i>Leptospira</i> species	Maculopapular eruption; conjunctival scleral hemorrhage in some cases
Lyme disease (Fig. A1-8)	<i>Borrelia burgdorferi</i> (sole cause in U.S.), <i>Borrelia afzelii</i> , <i>Borrelia garinii</i>	Papule expanding to erythematous annular lesion with central clearing (erythema migrans; average diameter, 15 cm), sometimes with central induration; sometimes with multiple secondary migrans lesions in some cases
Southern tick-associated rash illness (STARI, Master's disease)	Unknown (possibly <i>Borrelia lonestari</i> or other <i>Borrelia</i> spirochetes)	Similar to erythema migrans disease with several differences including: multiple secondary lesions less likely; lesions tending to be larger (average diameter, ~8 cm); more likely to be more likely
Typhoid fever (Fig. A1-9)	<i>Salmonella typhi</i>	Transient, blanchable erythematous macules and papules, 2–4 mm in diameter (rose spots)
Dengue fever ⁵ (Fig. A1-53)	Dengue virus (4 serotypes; flaviviruses)	Rash in 50% of cases; initial flushing; midway through illness, maculopapular rash, which spreads centrifugally to trunk and face; pruritus, hyperesquamous cases; after defervescence, extremities may occur
Rat-bite fever (sodoku)	<i>Spirillum minus</i>	Eschar at bite site; then bloody or red-brown rash involving extremities
Relapsing fever	<i>Borrelia</i> species	Central rash at end of febrile episode; petechiae in some cases
Erythema marginatum (rheumatic fever)	Group A <i>Streptococcus</i>	Erythematous annular papules occurring as polycyclic lesions over trunk, proximal extremities, and resolving within hours
Systemic lupus erythematosus (SLE) (Fig. A1-10, Fig. A1-11, Fig. A1-12)	Autoimmune disease	Macular and papular erythema on sun-exposed areas; discoid (local atrophy, scale, pigmentation, periungual telangiectasis; vasculitis sometimes causing palpable purpura; oral erosions)
Still's disease (Fig. A1-13)	Autoimmune disease	Transient 2- to 5-mm erythematous appearing at height of fever; proximal extremities; lesions

Table 1: Fever with rash – representative causes by eruption type

Eruption	Causes	Discriminating clue
Central maculopapular (viral)	Measles, rubella, enteroviruses, EBV mononucleosis, primary HIV, Zika	Measles: hairline downward, Koplik's spots ; rubella: clears from the original sites, postauricular adenopathy
Central maculopapular (bacterial/other)	Typhoid, leptospirosis, dengue, relapsing fever, rickettsial spotted fevers, Lyme disease	Typhoid: rose spots ; dengue: "saddleback" fever, petechiae after defervescence
Rat-bite fevers	<i>Spirillum minus</i> (sodoku), <i>Streptobacillus</i> (Haverhill fever)	Rash on palms, soles and extremities; arthritis in 50% (Haverhill)
Immune/autoimmune	Erythema marginatum (rheumatic fever), SLE, Still's disease	Marginatum: polycyclic lesions that evolve and resolve within hours; Still's: evanescent papules at the fever peak
Endovascular/other	Bacterial endocarditis, COVID-19	Osler's nodes and Janeway lesions; pernio or retiform purpura
Confluent desquamative erythema	Scarlet fever, Kawasaki disease, streptococcal and staphylococcal toxic shock syndrome, staphylococcal scalded-skin syndrome, exfoliative erythroderma	Scarlet fever: sandpaper skin, Pastia's lines, strawberry tongue; SSSS: Nikolsky's sign
Ulcer or eschar	Scrub typhus, rickettsialpox, anthrax	An eschar may be the only skin sign; in anthrax an ulcer or eschar may be the only manifestation

- Rickettsial spotted fever (*R. conorii*) occurs in India. It causes an eschar at the bite site and a maculopapular rash spreading from the proximal extremities to the trunk and face.
- Rubella in pregnancy causes severe congenital abnormalities, so pregnant women should avoid exposure.
- Vesicles from varicella or herpes simplex may evolve into pustules.
- Localised skin infections (cellulitis, impetigo) are excluded from this classification.

Definition of FUO (5 marks: algorithm follows)

- **FUO** requires all of the following:
 - fever $\geq 38.3^{\circ}\text{C}$ ($\geq 101^{\circ}\text{F}$) on at least two occasions
 - illness duration of at least **3 weeks**
 - no known immunocompromised state
 - diagnosis still uncertain after thorough history, examination and the **obligatory investigations**
- **IUO** is the same, except that body temperature is normal. Instead, CRP or ESR is raised on multiple occasions for at least 3 weeks. Causes and work-up are the same as for FUO.
- The older Petersdorf–Beeson definition (1961) required 3 weeks of fever and 1 week of inpatient evaluation.

Obligatory investigations

- Blood tests:
 - ESR, CRP, platelet count, leukocyte count with differential
 - haemoglobin, electrolytes, creatinine, total protein
 - ALP, ALT, AST, LDH, CK, ferritin, ANA, rheumatoid factor
 - protein electrophoresis
- Microbiology and imaging:
 - urinalysis
 - blood cultures (n = 3) and urine culture
 - chest X-ray
 - abdominal ultrasound
 - TST or IGRA

Table 2: Key investigations in FUO – what they add

Test	Finding	Meaning
Blood cultures	Prolonged incubation for fastidious organisms (HACEK)	Endocarditis; tell the lab when rare organisms are sought
TST/IGRA	Negative result	Does not exclude TB; may be indeterminate in miliary TB or immunosuppression
Liver biopsy	Granulomas; AFB smear, culture and PCR	Miliary TB if suspected; probably the highest yield
Cryoglobulins	Positive	A reasonable screening test in FUO
CSF examination	HSV-2, <i>Cryptococcus</i> , <i>M. tuberculosis</i>	Done when FUO is accompanied by headache
18F-FDG-PE T/CT	Raised uptake in vessels or inflammatory foci	Total diagnostic yield about 50%

Aetiology and epidemiology

- The chief causes of FUO are infections, non-infectious inflammatory diseases, malignancy and miscellaneous causes (including thermoregulatory disorders).
- **Infections:** abscesses, endocarditis, TB, typhoid and other salmonellosis, brucellosis, Q fever, leptospirosis, malaria, visceral leishmaniasis, dengue, chikungunya, HIV and EBV.
- **Non-infectious inflammatory:** SLE, Still's disease, vasculitis (giant cell arteritis, Takayasu arteritis, polyarteritis nodosa), sarcoidosis, autoinflammatory syndromes (familial Mediterranean fever).
- **Neoplasms:** lymphoma, leukaemia and haemophagocytic syndromes. The solid tumours most often causing FUO are breast, colon, hepatocellular, lung, pancreatic and renal cell carcinoma.
- **Miscellaneous:** drug fever, factitious fever, pulmonary embolism, thyroiditis.
- **Thermoregulatory:** central (hypothalamic dysfunction, brain tumour) and peripheral (hyperthyroidism, pheochromocytoma, heat stroke).

Table 22-2 — Harrison's 22e, pr.151. TABLE 22-2 Reported Causes of Fever of Unknown Origin (FUO)^a

[illegible]

*This table includes causes of FUO that have been described in the literature. *CAPS known as remittent-onset multisystem inflammatory disease, or NOMID; familial cold

Table 3: Pooled aetiology of FUO by region (Table 22-1, median %)

Region	Infections	Non-infectious inflammatory	Malignancy	No diagnosis
Western Europe	15.5	25	11	39.5
Middle East	66	15	7	8
Asia	42	19	13	17

- Infections dominate in Asia and the Middle East. Remaining undiagnosed is two to five times more likely in Europe than in Asia.
- Intra-abdominal abscesses and tumours are now found earlier by CT and ultrasound. Endocarditis is now found earlier by better blood culture and echocardiography.

Table 22-1 — Harrison's 22e, pr.149. TABLE 22-1 Etiology of FUO: Pooled Results of Large Studies Published in the Past 20 Years (2003–2023)

TABLE 22-1 Etiology of FUO: Pooled Results of Large Studies Published in the Past 20 Years (2003–2023)							
GEOGRAPHIC AREA	NO. OF COHORTS (INCLUSION PERIOD)	NO. OF PATIENTS	INFECTIONS, MEDIAN % (RANGE)	NONINFECTIOUS INFLAMMATORY DISEASES, MEDIAN % (RANGE)	MALIGNANCY, MEDIAN % (RANGE)	MISCELLANEOUS, MEDIAN % (RANGE)	NO DIAGNOSIS, MEDIAN % (RANGE)
Western Europe	12 (1995–2020)	2100	15.5 (4–36)	25 (17–33)	11 (3–30)	7.5 (0–16)	39.5 (26–54)
Other European and Turkey	15 (1984–2019)	1615	42 (26–74)	23 (12–38)	14 (4–19)	5 (2–18)	16 (0–35)
Middle East	3 (2009–2010) ^a	1289	66 (42–79)	15 (7–17)	7 (1–30)	1 (0–12)	8 (2–12)
Asia	39 (1994–2021) ^a	7191	42 (3–58)	19 (7–57)	13 (6–23)	6.5 (0–15)	17 (0–81)

Note: No studies from the Americas, Africa, or Oceania have been reported. Studies aimed at diagnostic methods were excluded.

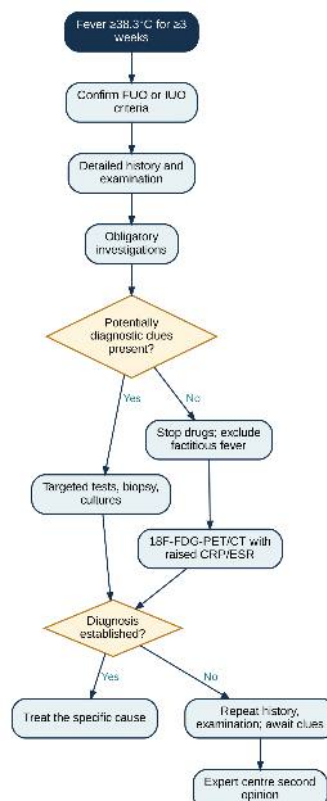
^aSome studies did not report an inclusion period.

For references, see supplementary material at accessmedicine.com/harrisons.

Diagnostic algorithm for FUO

- The approach is built on **potentially diagnostic clues (PDCs)**. These are found on history, examination and the obligatory tests.
- After the obligatory tests, make a short list of probable diagnoses. Then test only for those diseases.
- If no PDCs are found, repeat the history and examination regularly. Ask patients to return during a febrile episode.

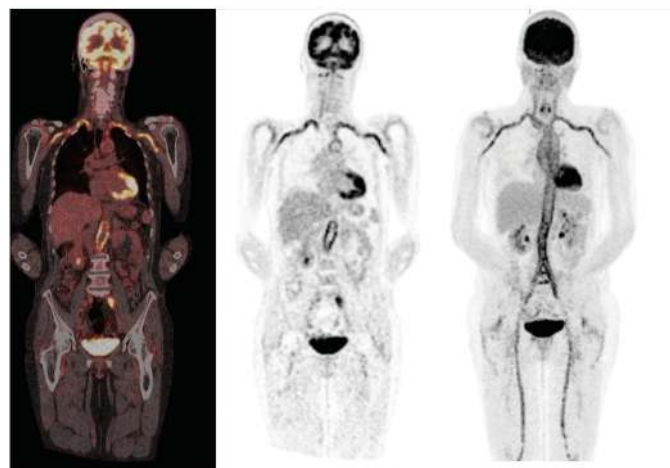
Flowchart 1: Approach to fever of unknown origin



Practical points in the work-up

- **Early steps:** rule out benign hyperthermia and factitious or fraudulent fever, especially if inflammatory markers are normal.
- **Drug fever:** stop all drugs, including non-prescription drugs and supplements. If fever persists beyond **72 h** after stopping, that drug is unlikely to be the cause.
- **Cultures:** more than three blood cultures or more than one urine culture is useless without PDCs. Repeat them only if the earlier samples were taken during antibiotics or within 1 week of stopping them.
- **Serology:** do not include microbiological serology without PDCs, because false positives outnumber true positives.
- **Low-yield tests without PDCs:** echocardiography, sinus radiography, GI radiology or endoscopy, bone marrow biopsy, liver biopsy and bronchoscopy.
- **Fundoscopy:** may exclude retinal vasculitis early on.
- **Giant cell arteritis:** present in up to **17%** of elderly patients with FUO. Temporal artery biopsy is still recommended for patients ≥ 55 years.
- **PET/CT:** FDG accumulates in malignant cells and in activated leukocytes. It cannot separate infection, sterile inflammation and malignancy.
- **Physiological uptake** in the brain, heart, bowel, kidney and bladder can mask lesions. A low-carbohydrate diet reduces cardiac uptake, which would otherwise obscure endocarditis.
- **Steroids and PET/CT:** glucocorticoids rapidly abolish FDG uptake in vasculitis and lymphoma. Stop or postpone them until after the scan.
- If the scan was done under the right conditions and was non-contributory, repeating it is of little value unless new signs appear.
- **Alternatives when PET/CT is unavailable:**
 - Gallium scintigraphy has a diagnostic yield of 21–54%, roughly one-third of cases.
 - Leukocyte scintigraphy has a yield of 8–31%, roughly one-fifth of cases.
 - Whole-body MRI had a yield comparable to PET/CT in one study.

Figure 22-2 — Harrison's 22e, pr.154. **FIGURE 22-2** 18F-FDG-PET/CT in a patient with FUO. This 72-year-old woman presented with a low-grade fever and severe fatigue of almost 3 months' duration. An extensive history was taken, but the patient had no specific complaints and had not traveled recently. Her previous history was unremarkable, and she did not use any drugs. Physical examination, including palpation of the temporal arteries, yielded completely



Management

GUIDELINE

No national or international guideline specific to FUO. Harrison's 22e, ch. 22.

- Treatment follows the **final diagnosis**.
- In unexplained FUO, most patients become symptom-free spontaneously.

- **Avoid empirical therapeutic trials** unless the patient is rapidly deteriorating. Trial drugs are antibiotics, antituberculars, NSAIDs, colchicine and IL-1 inhibitors.
- **Example:** large-vessel vasculitis with polymyalgia rheumatica responded within 1 week to prednisone 60 mg daily, which was tapered after 1 month.
- When all PDCs have been evaluated and nothing is found, waiting for new PDCs is better than more screening tests. Investigate further only if the patient deteriorates.
- A second opinion from an FUO expert centre should be considered. It gave a diagnosis in over half of unexplained cases, and a beneficial outcome in just under 70% of patients.
- Diagnostic delay often comes from failing to recognise PDCs in the available information.

PEARLS

- Fever is a **raised set point** driven by IL-1, TNF and IL-6. These induce PGE₂ in the preoptic hypothalamus.
- Fever differs from hyperthermia because fever is controlled by the hypothalamus.
- Koplik's spots appear in the first 2 days of measles and are pathognomonic.
- Measles rash starts at the hairline and spares palms and soles; rubella rash clears from the original sites as it spreads.
- Think scrub typhus, rickettsialpox or anthrax when an eschar is present.
- **FUO = $\geq 38.3^{\circ}\text{C}$, ≥ 3 weeks, immunocompetent, uncertain after obligatory tests.**
- Three blood cultures only; more than that is useless without clues.
- Do PET/CT while CRP/ESR is raised, and before glucocorticoids.
- Infections are the commonest FUO cause in Asia, and "no diagnosis" is commoner in Europe.
- Avoid empirical trials unless the patient is deteriorating.

14. Orthostatic hypotension — causes, diagnosis and management

ASKED 3* · Long answer

Asked in: Dec 2022 P-I Q5(b) (5 marks) · Oct 2024 P-II Q1(a) (1 marks) · Oct 2024 P-II Q1(b) (3 marks) · Oct 2024 P-II Q1(c) (6 marks) · Jun 2025 P-II Q7(a) (2 marks) · Jun 2025 P-II Q7(b) (3 marks)

Q: Pathophysiology and management of orthostatic hypotension. [5]

Q: Define orthostatic hypotension (OH). [1]

Q: Enumerate the causes of Neurogenic OH. [3]

Q: Describe the approach to the diagnosis and treatment of OH. [6]

Q: Define orthostatic hypotension. [2]

Q: Enlist various causes of orthostatic hypotension. [3]

SOURCE Harrison's 22e — Ch 23 Syncope, §Pathophysiology, Classification, Orthostatic Hypotension, Cardiac Syncope — pp. 156, 158–160

Harrison's 22e — Ch 446 Parkinson's Disease, §Laboratory Features (DLB) and Management of Nonmotor Features — pp. 3493, 3506

Harrison's 22e — Ch 451 Disorders of the Autonomic Nervous System — p. 3544

[W1] Consensus panel — Screening, diagnosis and treatment of neurogenic orthostatic hypotension and associated supine hypertension — 2017 (J Neurol 264:1567–1582) — <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5533816/>

Definition

- **Orthostatic hypotension (OH)** is a fall in systolic BP of ≥ 20 mmHg or diastolic BP of ≥ 10 mmHg after **3 min** of standing or head-up tilt on a tilt table.
- The consensus definition is the same: a sustained fall of ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic, or both, within 3 min of standing or head-up tilt to at least 60° .
- It is a manifestation of sympathetic vasoconstrictor (autonomic) failure.
- **Delayed OH** occurs beyond 3 min of standing and may reflect mild or early sympathetic adrenergic dysfunction.
- **Initial OH** occurs within 15 s of standing and resolves fully by 45 s.
 - It reflects a transient mismatch between cardiac output and peripheral vascular resistance.
 - It does not represent autonomic failure.

- **Neurogenic OH** is OH due to central or peripheral autonomic dysfunction. **Non-neurogenic OH** is due to volume depletion or drugs.

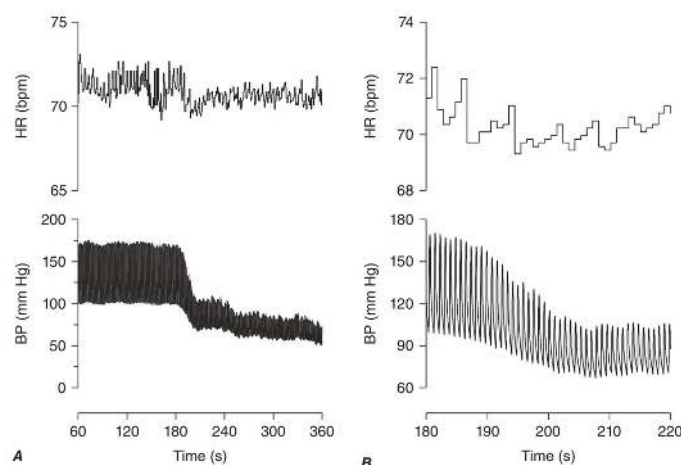
Why it matters

- Syncope due to OH carries increased mortality, related to age and comorbidity.
- OH prevalence rises with age because of reduced baroreflex responsiveness, decreased cardiac compliance and attenuated vestibulosympathetic reflex.
 - Reduced fluid intake and vasoactive drugs add to this in the elderly.
- It is more common in institutionalised than community-dwelling elderly.
- Profound falls in BP may be asymptomatic but put patients at risk of falls and injury.

Pathophysiology

- Standing pools **500–1000 mL** of blood in the legs, buttocks and splanchnic bed.
- Pooling reduces venous return and ventricular filling, so cardiac output and BP fall.
- Baroreceptors in the carotid sinus and aortic arch then raise sympathetic outflow and lower vagal activity.
 - This raises peripheral resistance, venous return and cardiac output, which limits the BP fall.
- In OH this reflex fails chronically, so hypotension and cerebral hypoperfusion follow.
- Cerebral blood flow is ~50–60 mL/min per 100 g and stays constant over perfusion pressures of 50–150 mmHg.
- Impaired consciousness occurs when flow falls to 25 mL/min per 100 g.
- Cessation of flow for 6–8 s causes loss of consciousness.
- Failure may be neurogenic (loss of sympathetic vasoconstriction) or non-neurogenic (reduced cardiac output or vascular tone from volume loss or drugs).
- Neurogenic OH typically shows no compensatory heart-rate rise despite hypotension.
 - In partial autonomic failure, the heart rate rises but not enough to maintain cardiac output.
- Mechanisms of **supine hypertension**:
 - It affects >50% of patients with autonomic failure in some series.
 - It is partly explained by baroreflex dysfunction with residual sympathetic outflow, especially in central autonomic degeneration.

Figure 23-3 — Harrison's 22e, pr.159. **FIGURE 23-3 A.** The gradual fall in blood pressure without a compensatory heart rate increase that is characteristic of orthostatic hypotension due to autonomic failure. Blood pressure and heart rate are shown >5 min (from 60 to 360 s) of an upright tilt on a tilt table. **B.** The same tracing expanded to show 40 s of the episode (from 180 to 220 s). BP, blood pressure; bpm, beats per minute; HR, heart rate.



Causes

- Classify as **neurogenic** (autonomic failure) and **non-neurogenic** (volume, drugs, cardiac).

Table 1: Causes of orthostatic hypotension

Category	Causes	Clue
Primary autonomic failure (synucleinopathies)	Parkinson's disease, dementia with Lewy bodies, pure autonomic failure, multiple system atrophy	Central α -synuclein aggregation; early prominent OH in "parkinsonism" suggests MSA
Secondary autonomic neuropathies	Diabetes, hereditary amyloidosis (familial amyloid polyneuropathy), AL amyloidosis, HSAN (especially type III), immune-mediated autonomic neuropathy, autoimmune autonomic ganglionopathy, Sjögren's syndrome, paraneoplastic neuropathy, HIV neuropathy	Small-fibre neuropathy with other autonomic deficits
Less frequent neuropathies	Vitamin B12 deficiency, neurotoxin exposure, HIV and other infections, porphyria	Systemic or toxic context
Postprandial hypotension	Large meals, carbohydrate-rich meals, alcohol, in autonomic failure and the elderly	Symptoms after meals
Iatrogenic (drugs)	α -blockers (hypertension, prostatic hypertrophy), diuretics, nitrates, other vasodilators and antihypertensives, tricyclics, phenothiazines	OH after starting or increasing a drug
Volume depletion	Diuresis, haemorrhage, vomiting, diarrhoea, reduced fluid intake	Tachycardic response; non-neurogenic

- Autonomic dysfunction of the bladder, bowel, sexual organs and sweating often accompanies neurogenic OH.

Table 23-2 — Harrison's 22e, pr.158. TABLE 23-2 Causes of Syncope

A. Neurally Mediated Syncope

Vasovagal syncope

Provoked fear, pain, anxiety, intense emotion, sight of blood, unpleasant

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Clinical features

- **Typical symptoms** are lightheadedness, dizziness and presyncope on sudden postural change.
- **Atypical or nonspecific symptoms:**
 - Generalised weakness, fatigue, cognitive slowing, leg buckling, headache.
 - Visual blurring from retinal or occipital ischaemia.
 - **Coat-hanger headache** (suboccipital, posterior cervical and shoulder pain) from neck muscle ischaemia, which may be the only symptom.
 - Orthostatic dyspnoea from V/Q mismatch at the lung apices.
 - Angina with normal coronary arteries.
- **Aggravating factors** are exertion, prolonged standing, heat and meals.
- Syncope is usually preceded by warning symptoms but may occur suddenly, which can mimic seizure or cardiac syncope.
- **Neurogenic clues:**
 - Heart rate rises <15 bpm on standing.
 - Non-neurogenic OH typically shows a rise of ≥ 15 bpm within 3 min.
 - Other autonomic deficits (bladder, bowel, sexual, sudomotor) accompany it.
- Supine hypertension is common in neurogenic OH.

Investigations and diagnostic approach

- Diagnose **stepwise**. Start with orthostatic BP and heart rate, then do detailed autonomic testing in selected cases.
- Measure BP and heart rate supine, then at 1 and 3 min of standing, or on head-up tilt of at least 60° .

Flowchart 1: Stepwise approach to suspected orthostatic hypotension

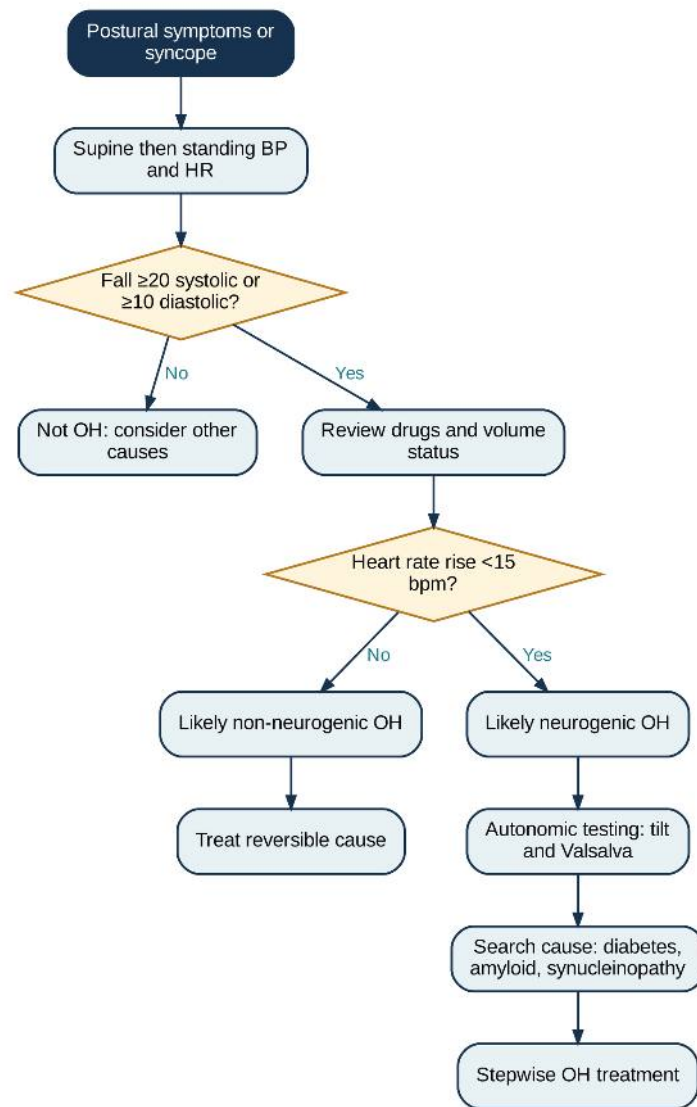
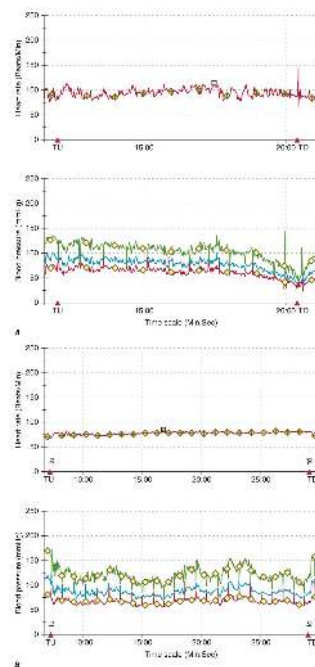


Table 2: Investigations in orthostatic hypotension

Test	Finding	Meaning
Orthostatic BP and HR (bedside)	Fall $\geq 20/10$ mmHg within 3 min	Confirms OH
Heart-rate response	Rise < 15 bpm	Neurogenic OH
Tilt-table test	Gradual BP fall without heart-rate rise	Autonomic failure
Tilt-table test (POTS pattern)	Heart rate rises ≥ 30 bpm (≥ 40 bpm if aged < 19) or exceeds 120 bpm within 10 min of standing or tilt, without sustained OH	POTS, not OH
Valsalva manoeuvre	Absent BP overshoot in phase 4	Sympathetic (adrenergic) failure
Plasma norepinephrine on standing	Reduced or absent rise (less than $\times 2$)	Neurogenic OH
Supine BP	Supine hypertension	Baroreflex failure with residual sympathetic outflow
Disease-specific tests	Glucose, B12, amyloid screen, immune and paraneoplastic work-up (clinical judgement)	Secondary neuropathies

Figure 451-4 — Harrison's 22e, pr.3544. **FIGURE 451-4** Examples of abnormal tilt responses. In each panel, the first tracing represents the heart rate, while the second represents the systolic, mean, and diastolic blood pressure responses. A. Progressive orthostatic hypotension leading to syncope. B. Neurogenic orthostatic hypotension (orthostatic hypotension without an adequate increase in heart rate). Notice the baseline supine hypertension (systolic 175 mmHg).



- The tracing in Figure 451-4B shows neurogenic OH with baseline supine hypertension (systolic 175 mmHg).

WORKED EXAMPLE

Patient: supine BP 140/80 mmHg, HR 72. At 3 min standing: BP 108/68 mmHg, HR 76.

1. Systolic fall = $140 - 108 = 32 \text{ mmHg}$ (≥ 20), so OH is present.
2. Diastolic fall = $80 - 68 = 12 \text{ mmHg}$ (≥ 10), which also meets criteria.
3. Heart-rate rise = $76 - 72 = 4 \text{ bpm}$ ($< 15 \text{ bpm}$), which suggests neurogenic OH.
4. The next step is to look for autonomic failure (diabetes, synucleinopathy, amyloid) and to check for supine hypertension.

Differential diagnosis

Table 3: Conditions mimicking or overlapping with OH

Condition	Feature	Distinguishing point
Vasovagal (neurally mediated) syncope	Premonitory pallor, sweating, nausea	Needs intact autonomic function; trigger-related
Cardiac syncope	Arrhythmia or structural disease	Abnormal ECG, exertional or sudden onset; high-risk features
Seizure	Aura, loss of consciousness $> 5 \text{ min}$, prolonged postictal drowsiness	Reorientation is immediate after syncope
Hypoglycaemia	Transient loss of consciousness in insulin-treated diabetics	Low glucose
POTS	Chronic ($> 3 \text{ months}$) orthostatic intolerance with heart rate rise $\geq 30 \text{ bpm}$ ($\geq 40 \text{ bpm}$ if aged < 19) or $> 120 \text{ bpm}$ within 10 min of standing	Tachycardia without sustained BP fall
Initial OH	Fall within 15 s, resolves by 45 s	Not autonomic failure

Management

GUIDELINE

International: Consensus panel — Screening, diagnosis and treatment of neurogenic orthostatic hypotension and associated supine hypertension — 2017 · Harrison's 22e, ch. 23 and ch. 446. No Indian national guideline.

- **Goal:** reduce symptom burden, not normalise standing BP.
- **Step 1: remove reversible causes**, usually vasoactive medications.
 - Stop drugs that cause or worsen OH.
 - Treat volume depletion (haemorrhage, vomiting, diarrhoea, excess diuresis).
- **Step 2: non-pharmacological measures first:**
 - Educate about staged moves from supine to upright.
 - Warn about the hypotensive effect of large meals.
 - Teach isometric counter-pressure manoeuvres.
 - Raise the head of the bed to reduce supine hypertension and nocturnal diuresis.
 - A 30° head-up tilt is used in Lewy body disease.
 - Expand intravascular volume with more dietary fluid and salt.
 - Rapid ingestion of 500 mL plain water often gives a short-term pressor response.
 - Physical therapy and home safety measures reduce fall injury.
- **Step 3: pharmacological** if non-drug measures fail:
 - **Fludrocortisone acetate.**
 - **Vasoconstrictors:** midodrine or droxidopa (L-dihydroxyphenylserine).
 - In Parkinson's disease, low doses of fludrocortisone or midodrine control most cases.
 - Droxidopa gives mild but transient benefit.
- **Step 4: refractory cases** may need pyridostigmine, atomoxetine, yohimbine, octreotide, desmopressin acetate or erythropoietin.
 - Vasopressin and erythropoietin are used in severe or refractory Parkinson's-related OH.
- **Postprandial hypotension:** avoid large, carbohydrate-rich meals and alcohol.
- **Supine hypertension** grading from the 2018 consensus:
 - Mild: SBP 140–159 or DBP 90–99 mmHg.
 - Moderate: SBP 160–179 or DBP 100–109 mmHg.
 - Use head-up sleeping and avoid treating OH to excess; the aim is symptom benefit, not standing BP.
- **Cause-directed therapy:** treat diabetes, amyloidosis or immune neuropathy as appropriate.
- **Follow-up:** review symptoms, falls, drugs and supine BP regularly.

Complications and prognosis

- Syncope, falls and injury, particularly in the elderly.
- Supine hypertension, which may follow treatment of OH or occur independently.
- Higher mortality in older, comorbid patients with OH-related syncope.
- Prognosis depends on the underlying cause; reversible drug or volume causes have the best outlook.

Recent advances

- The 2017 consensus emphasises a stepwise, symptom-focused approach and defines severity grades for supine hypertension.
- Droxidopa and midodrine are the vasoconstrictors named in Harrison's 22e.

PEARLS

- OH = fall of ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic within 3 min of standing or tilt.
- Heart-rate rise < 15 bpm suggests neurogenic OH; a larger rise suggests non-neurogenic OH.
- The commonest iatrogenic culprits are α -blockers, diuretics, nitrates, tricyclics and phenothiazines.
- Primary autonomic failure = synucleinopathies: PD, DLB, pure autonomic failure and MSA.
- Early prominent OH in a parkinsonian patient suggests MSA.
- Coat-hanger headache can be the only symptom.
- Treat supine hypertension with head-up sleeping, since $> 50\%$ of autonomic failure patients have it.
- Treatment order: stop drugs, then non-drug measures, then fludrocortisone or midodrine/droxidopa.
- The aim is symptom relief, not a normal standing BP.
- POTS is distinguished by a heart-rate rise of ≥ 30 bpm (≥ 40 bpm if aged < 19) or HR > 120 bpm within 10 min of standing, without sustained OH.

15. Syncope — causes, pathophysiology and evaluation

ASKED 2* · Long answer

Asked in: Jun 2021 P-I Q8 (10 marks) · Dec 2025 P-II Q3 (10 marks)

Q: Write down the causes, differential diagnosis and pathophysiology of syncope. [2+3+5] [10]

Q: Describe the etiology of syncope and evaluation of syncope in adults. [5+5] [10]

SOURCE Harrison's 22e — Ch 23 Syncope, §Prognosis, Pathophysiology, Classification, Features of Neurally Mediated Syncope, Initial Evaluation — pp. 155–156, 158, 161

Harrison's 22e — Ch 251 The Bradyarrhythmias, §Carotid Sinus Hypersensitivity and Neurally Mediated Bradycardia — p. 1920

Harrison's 22e — Ch 451 Disorders of the Autonomic Nervous System, §Tilt Table Testing — p. 3542

[W1] ESC — 2018 ESC Guidelines for the diagnosis and management of syncope — 2018 —

<https://www.escardio.org/guidelines/clinical-practice-guidelines/all-esc-practice-guidelines/syncope/> (with ACC/AHA/HRS 2017 syncope guideline)

Definition

- **Syncope** is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow.
- Onset is rapid, duration brief, and recovery spontaneous and complete.
- Syncope is one form of transient loss of consciousness (TLOC). It results from global cerebral hypoperfusion.
- Presyncope is the prodrome: lightheadedness or faintness, dizziness, weakness, fatigue, and visual and auditory disturbances.
- Loss of consciousness may also occur with no warning.
- Other causes of TLOC must be excluded: seizures, vertebrobasilar ischaemia, hypoxaemia and hypoglycaemia.

Why it matters

- Syncope accounts for $\sim 3\%$ of all emergency department visits and 1% of hospital admissions.
- The lifetime cumulative incidence is up to 40%.
- The age distribution is bimodal. The young peak is at 10–30 years, with a median around 15 years. Incidence rises sharply after 70 years.
- Prognosis depends on the cause:
 - Non-cardiac or unexplained syncope in the young has an excellent prognosis, with life expectancy unaffected.
 - Cardiac syncope carries an increased risk of sudden cardiac death and of death from other causes.
 - Mortality is also increased in orthostatic hypotension related to age and comorbidity.
- The ESC 2018 syncope guideline was the first to address the emergency department explicitly.

Causes (aetiology)

- Syncope has three broad categories: neurally mediated (reflex or vasovagal), orthostatic hypotension, and cardiac.

- The clinical features, mechanisms, treatment and prognosis differ markedly among the three.
- Neurally mediated syncope is the commonest cause in population studies, and is commoner in women.
- Cardiovascular causes are next in frequency, especially in the ED and in older patients.

Table 1: Causes of syncope (Harrison's Table 23-2)

Category	Causes	Clue
Vasovagal	Fear, pain, anxiety, intense emotion, sight of blood, unpleasant sights and odours, orthostatic stress	Trigger plus autonomic prodrome
Situational: pulmonary	Cough, wind-instrument player's, weightlifter's, sneeze syncope, airway instrumentation	Raised intrathoracic pressure or hyperventilation
Situational: urogenital and GI	Postmicturition, swallow, defecation syncope, glossopharyngeal neuralgia, rectal examination	Specific local stimulus
Situational: cardiac, carotid, ocular	Bezold-Jarisch reflex, cardiac outflow obstruction, carotid sinus sensitivity or massage, ocular pressure or surgery	Neck or eye stimulus
Primary autonomic failure	Parkinson's disease, Lewy body dementia, pure autonomic failure, multiple system atrophy	Chronic OH, "synucleinopathies"
Secondary autonomic failure	Diabetes, hereditary and AL amyloidosis, HSAN, autoimmune autonomic ganglionopathy, Sjögren's, paraneoplastic, HIV neuropathy	Peripheral autonomic neuropathy
Other OH	Postprandial hypotension, drugs, volume depletion	Reversible
Cardiac arrhythmia	Sinus node dysfunction, AV dysfunction, SVT, VT, inherited channelopathies	Palpitations, exertion, ECG
Cardiac structural	Valvular disease, myocardial ischaemia, obstructive and other cardiomyopathies, atrial myxoma, pericardial effusion and tamponade	Murmur, exertional, low EF

- Drugs that cause sinus node dysfunction and bradycardia can also provoke syncope. Examples are beta-blockers, clonidine, methyl dopa, non-dihydropyridine calcium channel blockers, amiodarone, sotalol, digoxin and lithium.
- Reversible medical causes of sinus bradycardia include hypothyroidism, sleep apnoea, hypoxia, hypothermia, raised intracranial pressure and myocarditis.
- Other causes of impaired cardiac output are massive pulmonary embolus, decreased effective circulating volume and increased thoracic pressure.

Table 23-2 — Harrison's 22e, pr.158. TABLE 23-2 Causes of Syncope

A. Neurally Mediated Syncope

Vasovagal syncope

Provoked fear, pain, anxiety, intense emotion, sight of blood, unpleasant

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Pathophysiology

Upright posture and reflex compensation

- Standing pools 500–1000 mL of blood in the legs, buttocks and splanchnic circulation.
- Venous return and ventricular filling fall, so cardiac output and BP fall.
- Baroreceptors in the carotid sinus and aortic arch trigger a reflex. Sympathetic outflow rises and vagal activity falls.
- The reflex raises peripheral resistance, venous return and cardiac output, and limits the fall in BP.
- If the reflex fails, hypotension and cerebral hypoperfusion follow. The failure is chronic in orthostatic hypotension and transient in neurally mediated syncope.

Cerebral blood flow thresholds

- Autoregulation depends on myogenic factors, local metabolites and, to a lesser extent, autonomic neurovascular control. Its latency is 5–10 s.
- Normal cerebral blood flow is 50–60 mL/min per 100 g. It stays constant over perfusion pressures of 50–150 mmHg.

- Cessation of flow for **6–8 s** causes loss of consciousness.
- Consciousness is impaired when flow falls to **25 mL/min per 100 g**.
- A systolic BP of **~50 mmHg or lower** usually produces syncope.

Determinants of BP

- BP depends on cardiac output and systemic vascular resistance.
- Cardiac output falls with:
 - low circulating volume
 - raised thoracic pressure
 - massive PE
 - brady- and tachyarrhythmias
 - valvular disease
 - myocardial dysfunction
- Vascular resistance falls with:
 - central and peripheral autonomic disease
 - sympatholytic drugs
 - transiently during neurally mediated syncope
- Increased cerebral vascular resistance also contributes, most often from hyperventilation-induced hypocarbia.

Mechanism by type

- Neurally mediated syncope is the final pathway of a central and peripheral reflex arc.
 - Parasympathetic outflow rises and the sympathetic system is inhibited. This produces bradycardia, vasodilation and reduced output.
 - A functioning autonomic nervous system is necessary.
 - Afferent pathways converge on the medullary central autonomic network.
 - Hyperventilation and raised intrathoracic pressure are central to many situational reflex syncope.
- By efferent pathway:
 - **Vasodepressor**: predominant sympathetic vasoconstrictor failure.
 - **Cardioinhibitory**: bradycardia or asystole from vagal outflow.
 - **Mixed**: both vagal and sympathetic changes.
- Orthostatic hypotension in autonomic failure reflects chronic impairment of the homeostatic reflexes.
- Cardiac syncope arises from arrhythmia or structural disease that lowers output.
- EEG during syncope shows a "slow-flat-slow" or a "slow" pattern. The flat phase marks more severe hypoperfusion. No seizure discharges occur.

Clinical features

Neurally mediated syncope

- Prodrome: dizziness, lightheadedness and fatigue, plus diaphoresis, pallor, palpitations, nausea, hyperventilation and yawning.
- Predisposing factors: motionless upright posture, warm environment, volume depletion, alcohol, hypoxaemia, anaemia, pain, the sight of blood, venipuncture and emotion.
- During the event, myoclonus (arrhythmic, multifocal) may mimic a seizure.
 - The eyes are open and deviate upward. The pupils are dilated.
 - Grunting or stertorous breathing and urinary incontinence may occur.
 - Faecal incontinence and postictal confusion are rare.
- A family history in first-degree relatives is common in the young.

Table 2: Discriminating features of the three groups

Feature	Neurally mediated	Orthostatic hypotension	Cardiac
Autonomic function	Intact, transient failure of reflex	Chronically impaired reflexes	Not primary
Typical patient	Young, female predominance	Older, institutionalised, drugs, neuropathy	Older, ED, structural disease
Trigger or setting	Emotion, pain, standing, situational stimuli	Standing, postprandial, volume depletion	Exertion, supine, palpitations
Prognosis	Excellent in the young	Mortality raised with comorbidity	Sudden death risk raised

Differential diagnosis (other causes of TLOC)

Table 3: Syncope mimics and how to separate them

Condition	Discriminating point
Seizure	Syncopal myoclonus is brief, but EEG shows no seizure discharges, and postictal confusion is rare
Hypoglycaemia	Tremor, palpitations, anxiety, diaphoresis, hunger and paraesthesiae; hunger is not a premonitory feature of syncope
Cataplexy	Consciousness preserved, triggered by anger or laughter, lasts 30 s–2 min, no premonitory symptoms; occurs in 60–75% of narcolepsy
Falls (vestibular, cerebellar, extrapyramidal, gait)	Clinical interview and eyewitness account usually differentiate; dementia makes this hard
Head trauma or concussion	Amnesia or altered consciousness confuses the picture
Psychogenic (anxiety, panic, depression, somatisation)	Frequent faints without prodrome, rarely injured, no haemodynamic change
Vertebrobasilar ischaemia, hypoxaemia	Listed as other causes of TLOC to be excluded

- Hypoglycaemia is harder to recognise in strict glycaemic control, because repeated episodes blunt the warning symptoms.
- In vasovagal syncope from emotion, hypotension and sometimes bradycardia occur. These are absent in psychogenic episodes.

Evaluation

Goals of the initial evaluation

- Decide whether the TLOC was syncope.
- Identify the cause.
- Assess the risk of recurrence and serious harm.
- The ESC 2018 guideline recommends structured risk stratification to guide admission and telemetry.
- It also gives significant attention to excluding sustained VT as the cause.

History and examination

- Take a detailed history, question eyewitnesses and do a full physical and neurological examination.
- Cellphone video of the spell helps.
- Measure BP and HR supine and after **3 min of standing** to look for orthostatic hypotension.
- High-risk features on history:
 - new chest discomfort, abdominal pain, dyspnoea or headache
 - syncope during exertion or while supine
 - sudden palpitations followed by syncope
 - severe coronary or structural heart disease
- High-risk features on examination:
 - unexplained SBP <90 mmHg
 - suspected GI haemorrhage

- persistent bradycardia **<40/min**
- an undiagnosed systolic murmur
- The initial assessment identifies a cause in **~50%** of patients.

Table 4: High-risk features needing hospitalisation or intensive evaluation (Table 23-1)

Domain	Features
Clinical	Chest pain suggesting ischaemia, features of heart failure, syncope at rest or on exercise, palpitations at the time of syncope, family history of sudden death
Structural	Moderate or severe valvular or structural heart disease
ECG	Ischaemia, prolonged QT >500 ms, sinus pauses or repetitive SA block, persistent sinus bradycardia, bi- or trifascicular block or QRS ≥120 ms, AF, nonsustained VT, pre-excitation, Brugada pattern
History	Ventricular arrhythmias

Table 23-1 — Harrison's 22e, pr.156. **TABLE 23-1 High-Risk Features Indicating Hospitalization or Intensive Evaluation of Syncope**

TABLE 23-1 High-Risk Features Indicating Hospitalization or Intensive Evaluation of Syncope

Chest pain suggesting coronary ischemia
 Features of congestive heart failure
 Moderate or severe valvular disease
 Moderate or severe structural cardiac disease
 Electrocardiographic features of ischemia
 History of ventricular arrhythmias
 Prolonged QT interval (>500 ms)
 Repetitive sinoatrial block or sinus pauses
 Persistent sinus bradycardia
 Bi- or trifascicular block or intraventricular conduction delay with QRS duration ≥120 ms
 Atrial fibrillation
 Nonsustained ventricular tachycardia
 Family history of sudden death
 Preexcitation syndromes
 Brugada pattern on electrocardiogram
 Palpitations at time of syncope
 Syncope at rest or during exercise

Investigations

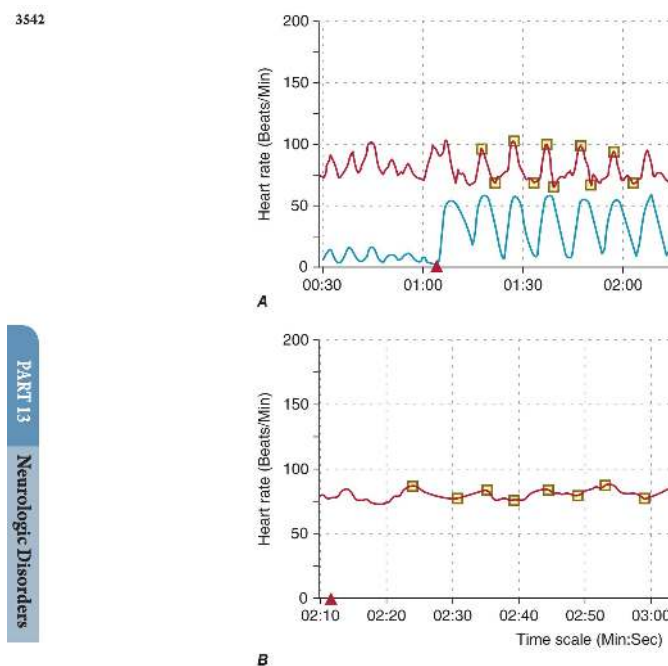
Table 5: Investigations in syncope

Test	Indication or finding	Meaning
ECG	Suspected arrhythmia or heart disease; bradyarrhythmia or tachyarrhythmia, AV block, ischaemia, old MI, long QT, bundle branch block	Cardiac cause and mortality risk
Blood tests	Rarely helpful; use for suspected MI, anaemia or secondary autonomic failure	Targeted only
Echocardiography	Cardiac history, abnormal examination or ECG; aortic stenosis, HCM, tumours, aortic dissection, tamponade	Structural cause and EF-based risk
In-hospital ECG monitoring	High chance of life-threatening arrhythmia, e.g. severe CAD, NSVT, trifascicular block, long QT, Brugada pattern	Capture arrhythmia
Holter	Near-daily syncope	Frequent events
External or implantable loop recorder	Low risk of sudden death; external if episodes >1/month, implantable if rarer	Correlate rhythm and symptom

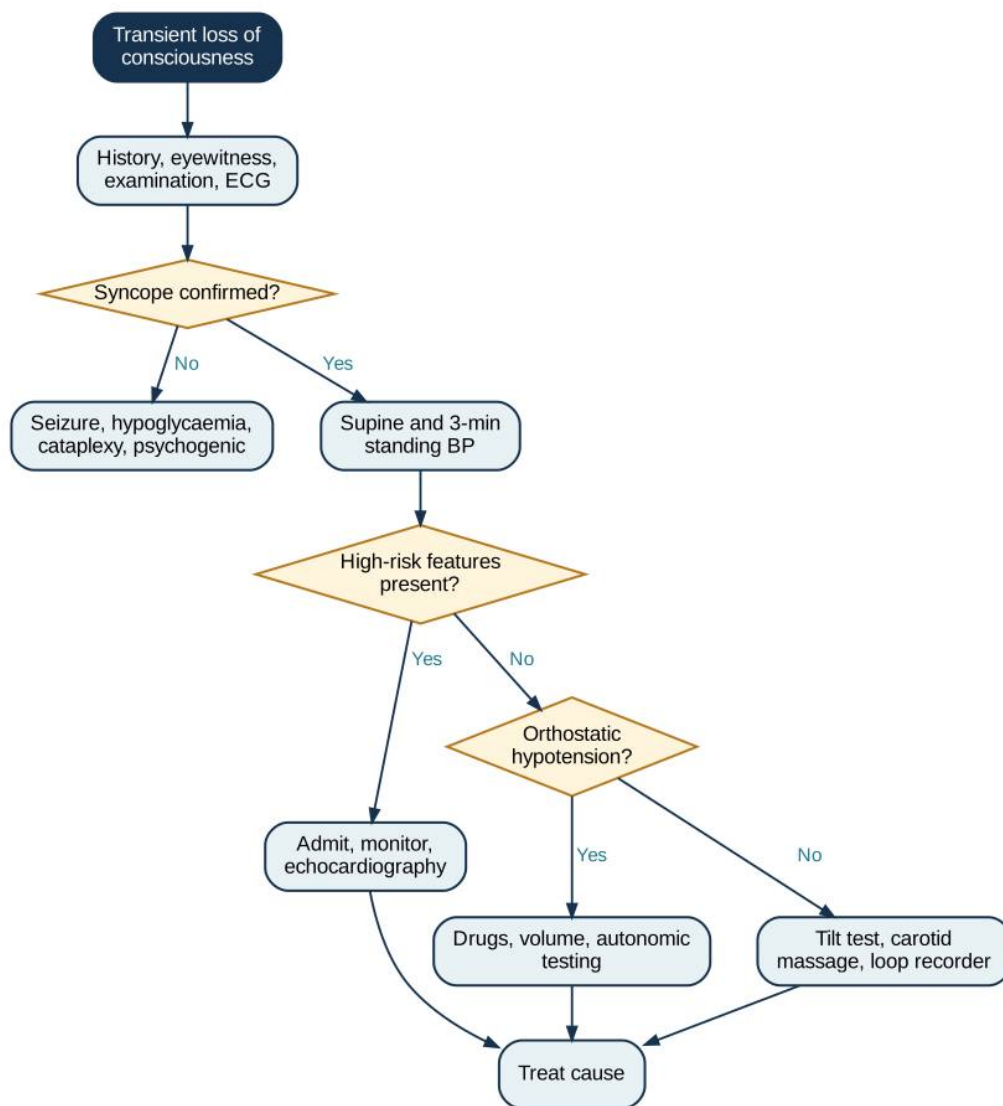
Test	Indication or finding	Meaning
Treadmill test	Syncope during or after exercise	Exercise-induced arrhythmia or vasodilation
Tilt-table test	Tilt 60–70° for 30–40 min; nitroglycerin or isoproterenol provocation if negative	Separates OH from reflex syncope; provocation raises sensitivity, lowers specificity
Autonomic function tests	Heart-rate variability to deep breathing, Valsalva, QSART, thermoregulatory sweat test	Objective autonomic failure
Carotid sinus massage	Suspected carotid syncope, or >40 years with recurrent unexplained syncope	Carotid sinus hypersensitivity
Electrophysiology study	Structural heart disease with ECG abnormality and negative non-invasive tests	Rarely used, low sensitivity and specificity
Psychiatric screening	Recurrent unexplained syncope	Psychogenic cause

- Loop monitoring should ideally last at least twice the interspell duration.
- Carotid massage should be done under continuous ECG and BP monitoring. Avoid it with carotid bruits, plaques or stenosis.
- The Valsalva ratio reflects the parasympathetic arm of the baroreflex.
- Heart-rate variation to deep breathing and the Valsalva ratio are reduced in autonomic failure.
- QSART and the thermoregulatory sweat test help localise the lesion:
 - Both absent indicates a postganglionic lesion.
 - A preserved QSART with anhidrosis on the sweat test indicates a preganglionic lesion.

Figure 451-2 — Harrison's 22e, pr.3542. FIGURE 451-2 Examples of normal (A) and reduced (B) heart rate variability to deep breathing.



Flowchart 1: Stepwise evaluation of syncope



Management

GUIDELINE

India: no national guideline · International: ESC — 2018 ESC Guidelines for the diagnosis and management of syncope — 2018; ACC/AHA/HRS — 2017 syncope guideline — 2017 · Treatment details: Harrison's 22e, ch. 23

- Management is directed at the cause and the risk category.
- Neurally mediated syncope:
 - Cornerstones are reassurance, education, avoidance of triggers and plasma volume expansion with fluid and salt.
 - Isometric counterpressure manoeuvres (leg crossing, handgrip, arm tensing, abdominal and leg muscle tensing) raise BP. Abdominal and leg tensing is the most effective.
 - They help most in patients with a long prodrome, and a randomised trial supports them.
 - In refractory cases, fludrocortisone, vasoconstrictors and beta-blockers are used by experts. Only **midodrine** has been effective in international multicentre RCTs.
 - Pacemakers are rarely beneficial.
 - Dual-chamber closed-loop pacing reduced recurrence in a sham-controlled trial. It enrolled patients >40 years with frequent syncope and a cardioinhibitory response on tilt test.
 - Carotid hypersensitivity with a predominant cardioinhibitory component responds to pacing.
 - Trials of pacing in drug-refractory vasovagal syncope gave mixed results.
- Cardiac syncope:
 - In sinus node disease, first remove reversible causes such as MI, electrolyte disturbance, drugs and hypothyroidism.

- If a bradycardic drug is unavoidable, a pacemaker may be indicated.
- In tachy-brady syndrome, control of the tachycardia by drugs or ablation can prevent bradycardia events. Pacing may be needed if control fails.
- Orthostatic hypotension: review drugs and correct volume depletion (Table 23-2).

Complications and prognosis

- Injury from falls. Recurrent episodes can occur.
- Cardiac syncope: risk of sudden cardiac death.
- Syncope from orthostatic hypotension in the elderly is associated with higher hospitalisation and mortality.

Pearls

PEARLS

- Syncope = global cerebral hypoperfusion; flow stopped for **6–8 s** causes loss of consciousness.
- SBP falling to **~50 mmHg** typically produces syncope.
- Always check lying and **3-min standing BP**.
- History, examination and ECG identify the cause in **~50%**.
- Exertional or supine syncope, palpitations beforehand, QTc **>500 ms**, and QRS ≥ 120 ms or trifascicular block mandate admission or monitoring.
- Syncopal myoclonus and incontinence do not make a seizure. EEG shows no seizure discharges.
- Hunger and tremor point to hypoglycaemia. Preserved consciousness with laughter or anger triggers points to cataplexy.
- Midodrine is the only drug with RCT proof in refractory reflex syncope.
- Pacing helps only selected cardioinhibitory patients (>40 years, frequent recurrences).
- Tilt provocation with nitroglycerin or isoproterenol raises sensitivity but lowers specificity.

16. Vertigo — approach, peripheral vs central and treatment

ASKED 1* • Long answer

Asked in: Jun 2022 P-II Q10(a) (4 marks) • Jun 2022 P-II Q10(b) (3 marks) • Jun 2022 P-II Q10(c) (3 marks)

Q: How do you approach a case of vertigo? [4]

Q: What are the differentiating features between peripheral and central vertigo. [3]

Q: Discuss the treatment of vertigo. [3]

SOURCE Harrison's 22e — Ch 24 Dizziness and Vertigo, §Approach to the Patient; Differential Diagnosis and Treatment; Vestibular Migraine — pp. 162–165

[W1] Bárány Society, Committee for Classification of Vestibular Disorders — International Classification of Vestibular Disorders (ICVD), including Benign paroxysmal positional vertigo: diagnostic criteria — <https://pubmed.ncbi.nlm.nih.gov/26756126/>

Definition and terminology

- **Dizziness** is an imprecise symptom covering vertigo, light-headedness, faintness and imbalance.
- **Vertigo** is a sense of spinning or other motion. It may be physiological (during or after sustained head rotation) or pathological (vestibular dysfunction).
- The Bárány Society (ICVD) defines vertigo as a sensation of self-motion when no motion is present, or distorted self-motion during a normal head movement.
- ICVD defines dizziness as disturbed or impaired spatial orientation without a false or distorted sense of motion.
- ICVD lists four main vestibular symptoms: dizziness, vertigo, vestibulovisual symptoms and postural symptoms.
- **Light-headedness** classically means presyncope from brain hypoperfusion, but patients use the word non-specifically.
- Patients often cannot separate these sensations, and the words they choose do not reliably indicate the cause.

Why it matters

- Vertigo implies an acute asymmetry of vestibular input from the two labyrinths or their central pathways.
- Symmetric bilateral vestibular hypofunction causes imbalance but **no vertigo**.
- Acute central vertigo is a **medical emergency** because of possible life-threatening stroke or haemorrhage.
- Three questions guide the evaluation:
 - Is it dangerous (arrhythmia, TIA/stroke)?
 - Is it vestibular?
 - If vestibular, is it peripheral or central?

Immediate stabilisation and red flags

- First exclude dangerous causes. Look for cardiac dysrhythmia, orthostatic hypotension, medication effects and other causes of brain hypoperfusion.
- Consider faintness and syncope in brief episodes of dizziness or dizziness on standing.
- In acute prolonged vertigo, look for diplopia, weakness or numbness, and dysarthria, which point to a central lesion.
- Older patients with vascular risk factors and an acute vestibular syndrome need evaluation for stroke even without specific central signs.
- Central causes cannot always be excluded on symptoms and examination alone.

Focused history (approach, step 1)

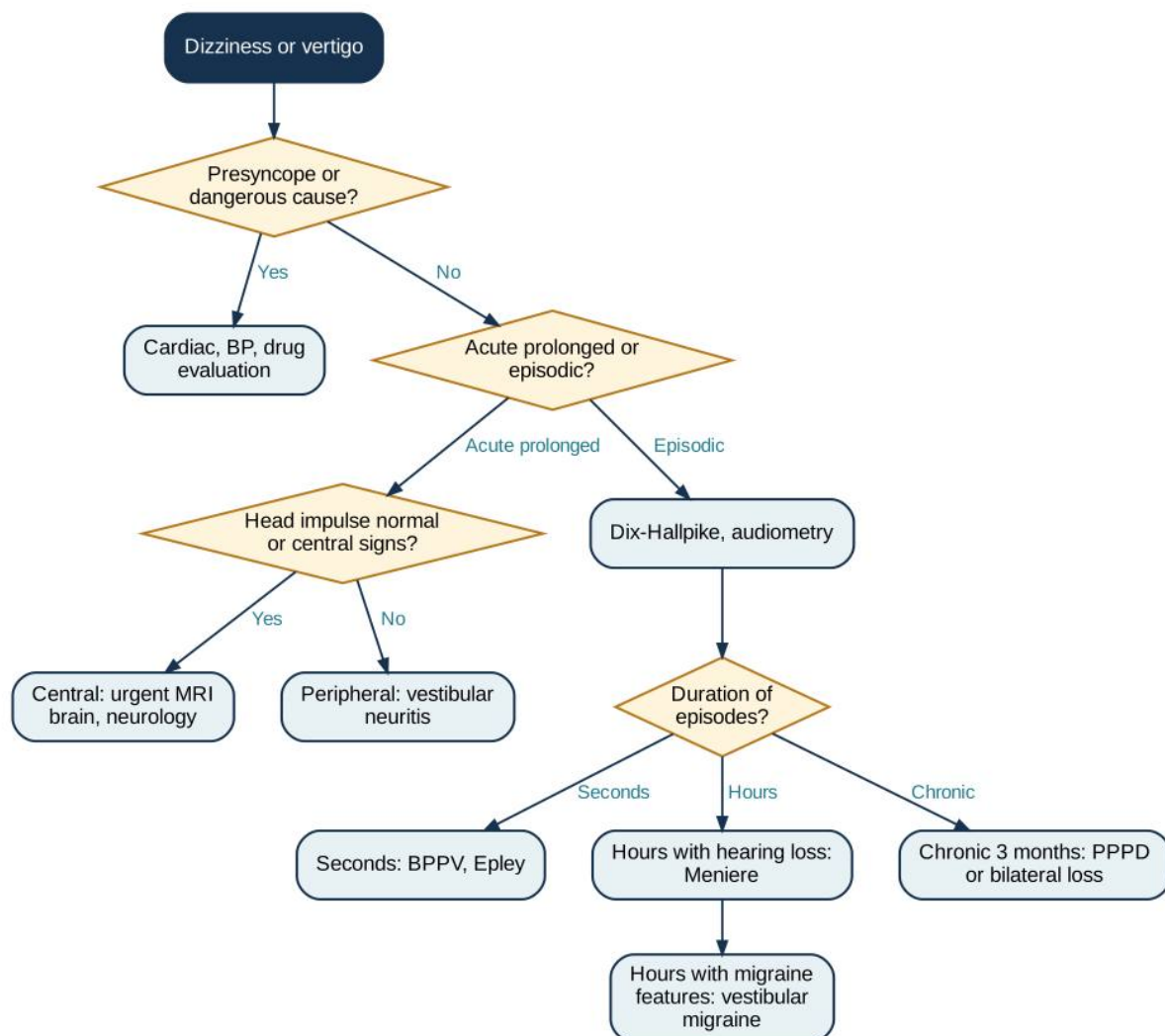
- Establish the **nature of the symptom** first: true vertigo versus presyncope versus imbalance.
- Symptom description alone is unreliable, so focus on the following:
 - whether this is the first attack
 - the duration of this and any prior episodes
 - provoking factors
 - accompanying symptoms
- **Timing** is the key discriminator:
 - Seconds: BPPV and orthostatic hypotension, both provoked by position change relative to gravity.
 - Minutes: posterior-circulation TIA (migraine and others also possible).
 - Hours: vestibular migraine and Ménière's disease.
 - Days: acute vestibular syndrome (vestibular neuritis, or central causes such as stroke).
- **Triggers:** rolling over in bed favours BPPV over orthostatic hypotension.
- **Associated symptoms:**
 - Unilateral hearing loss, ear pain, pressure, fullness or new tinnitus point to a peripheral cause.
 - Auditory pathways become bilateral early in the brainstem, so central lesions rarely cause unilateral deafness. The exception is a lesion near the root entry zone of the auditory nerve.
 - Diplopia, numbness and limb ataxia suggest a brainstem or cerebellar lesion.
- Also ask about drugs (e.g., aminoglycosides cause ototoxicity), migraine history, anxiety and past vestibular illness.

Examination (approach, step 2)

- The neurological examination is essential. Focus on eye movements, vestibular function and hearing.
- **Ocular motility:**
 - Peripheral eye-movement disorders are usually disconjugate.
 - Check pursuit and saccades. Poor pursuit or dysmetric saccades indicate central, often cerebellar, pathology.
 - A cover test showing vertical misalignment suggests a brainstem or cerebellar lesion.
- **Spontaneous nystagmus** is usually of the jerk type, with a slow phase and a fast (quick) phase that resets the eyes.
- Nystagmus easily seen in the light is probably central, except in acute vestibulopathy such as vestibular neuritis.
- Cerebellar-pathway nystagmus is of two types:

- **Downbeat** (vertical, fast phase down).
- **Gaze-evoked** (horizontal, changes direction with gaze).
- Peripheral lesions typically cause **unidirectional horizontal** nystagmus.
- Frenzel goggles or infrared video goggles reduce visual fixation and help detect peripheral nystagmus.
- **Head impulse test:**
 - This is the most useful bedside test of peripheral vestibular function.
 - Small-amplitude ($\sim 20^\circ$) rapid head rotations are given while the patient fixates on a target.
 - A deficient VOR produces a catch-up saccade in the opposite direction.
 - Catch-up saccades after rotation to one side indicate unilateral hypofunction. Catch-up saccades in both directions indicate bilateral hypofunction.
 - A **normal** head impulse test in acute vertigo makes a peripheral lesion unlikely.
- **Dix–Hallpike manoeuvre** (all patients with episodic or positional dizziness):
 - Start with the patient sitting, head turned 45° .
 - Lower the patient supine with the head extended about 20° and watch the eyes.
 - Transient **upbeating-torsional nystagmus** confirms posterior canal BPPV.
 - If no nystagmus appears after 15–20 s, sit the patient up and repeat with the head turned to the other side.
- **Dynamic visual acuity:** a drop of **more than one line** on a Snellen or near card during 1–2 Hz head rotation indicates vestibular dysfunction.
- Look for a Romberg sign and examine gait for bilateral loss.

Flowchart 1: Diagnostic approach to a patient with vertigo/dizziness



Differentiating peripheral from central vertigo

Table 1: Peripheral versus central vertigo

Feature	Peripheral	Central
Nystagmus direction	Unidirectional, fast phase away from the lesioned ear	Changes direction with gaze
Nystagmus pattern	BPPV: transient mixed vertical-torsional	Pure vertical or pure torsional
Special types	Horizontal, unidirectional	Downbeat, gaze-evoked
Visual fixation	Inhibits nystagmus	Does not suppress nystagmus
Visibility in light	Usually needs Frenzel goggles; easily visible only in acute vestibulopathy	Easily seen in light
Head impulse test	Abnormal (catch-up saccade) toward the lesion	Normal; absence of the head impulse sign in acute prolonged vertigo suggests central cause
Hearing	Unilateral hearing loss, tinnitus, aural fullness	Usually preserved; loss only if lesion near the root entry zone
Other neurological signs	Absent	Diplopia, dysarthria, limb ataxia, weakness, numbness
Eye movements	Pursuit and saccades normal	Poor pursuit or dysmetric saccades
Typical causes	Neuritis, BPPV, Ménière's disease, schwannoma	Stroke, haemorrhage, demyelination, tumour, degeneration

Table 24-1 — Harrison's 22e, pr.163. TABLE 24-1 Features of Peripheral and Central Vertigo

- Nystagmus from an acute peripheral lesion is unidirectional, with fast phases beating away from the ear with the lesion. Nystagmus that changes direction with gaze is due to a central lesion.
- Transient mixed vertical-torsional nystagmus occurs in benign paroxysmal positional vertigo (BPPV), but pure vertical or pure torsional nystagmus is a central sign.
- Nystagmus from a peripheral lesion may be inhibited by visual fixation, whereas central nystagmus is not suppressed.
- Absence of a head impulse sign in a patient with acute prolonged vertigo should suggest a central cause.
- Unilateral hearing loss suggests peripheral vertigo. Findings such as diplopia, dysarthria, and limb ataxia suggest a central disorder.

Ancillary investigations

- Choose tests by history and examination.
- **Audiometry** whenever a vestibular disorder is suspected.
 - Unilateral sensorineural loss supports a peripheral disorder such as schwannoma.
 - Predominantly low-frequency loss is characteristic of Ménière's disease.
- **Videonystagmography** records spontaneous and positional nystagmus.
- **Caloric testing** compares the two horizontal canals. **Video head-impulse testing** assesses all six canals.
- **Vestibular evoked potentials** assess otolith reflexes.
- Recording of saccades and pursuit evaluates central ocular-motor function.
- **MRI brain** in all suspected central vestibular disorders.
- **Gadolinium MRI of the internal auditory canals** for unexplained unilateral hearing loss or vestibular hypofunction, to exclude schwannoma.

Differential diagnosis by syndrome

Table 2: Common causes of vertigo by timing and features

Disorder	Duration	Key features
BPPV	<1 min, typically 15–20 s	Positional trigger; upbeating-torsional nystagmus on Dix–Hallpike
Orthostatic hypotension	Seconds	Provoked by standing, not by rolling in bed
Vestibular neuritis	Days	Constant vertigo, nausea, vomiting, oscillopsia, imbalance; persists with the head still
Ménière's disease	Hours	Vertigo, hearing loss, aural pain, pressure or fullness; low-frequency loss
Vestibular migraine	Minutes to hours; imbalance days to weeks	Photophobia, phonophobia, aura, motion sensitivity; often little headache
Posterior-circulation TIA	Minutes	Associated brainstem symptoms; vascular risk factors
Vestibular schwannoma	Progressive	Slow unilateral sensorineural loss, usually no vertigo; abnormal head impulse toward affected side
Bilateral vestibular hypofunction	Chronic	Imbalance, worse in the dark; oscillopsia; no vertigo
PPPD	≥3 months	Fluctuating dizziness, worse on standing and in complex visual environments; normal vestibular testing

Management of vertigo

GUIDELINE

India: — • International: Bárány Society — International Classification of Vestibular Disorders (definitions and BPPV criteria); management: Harrison's 22e, ch. 24

- **Principle:** treat according to the underlying diagnosis. Simply suppressing dizziness with drugs is often unhelpful and may prolong recovery.

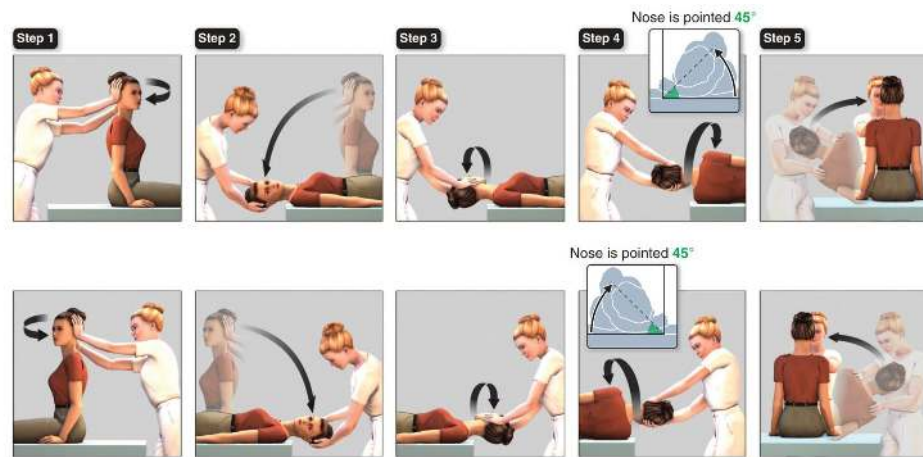
Acute vestibular neuritis

- Most patients recover spontaneously. Chronic dizziness, motion sensitivity and disequilibrium may persist.
- Early glucocorticoids have an uncertain role because studies gave disparate results.
- Antivirals have no proven benefit. Use them only if herpes zoster oticus (Ramsay Hunt syndrome) is suspected.
- Vestibular suppressants may reduce acute symptoms but should be avoided after the first several days. They impede central compensation.
- Resume normal activity early. Directed vestibular rehabilitation may accelerate recovery.

BPPV

- Treat with **repositioning manoeuvres**, which use gravity to clear otoconia from the canal.
- Posterior canal BPPV: the **Epley manoeuvre** is the most commonly used.
- The Bárány Society notes that appropriate repositioning manoeuvres both treat BPPV and help confirm the diagnosis.
- Steps of the modified Epley manoeuvre:
 - Seated, turn the head 45° toward the affected ear.
 - Lower to head-hanging and hold at least 30 s, until nystagmus disappears.
 - Turn the head 90° to the other side without lifting it, and hold 30 s.
 - Roll onto the side while turning the head a further 90° (nose down 45°), and hold 30 s.
 - Sit up. After a brief rest, repeat to confirm success.
- Refractory cases can be taught a home variant of the manoeuvre.

Figure 24-1 — Harrison's 22e, pr.164. **FIGURE 24-1** Modified Epley maneuver for treatment of benign paroxysmal positional vertigo of the right (top panels) and left (bottom panels) posterior semicircular canals. Step 1. With the patient seated, turn the head 45 degrees toward the affected ear. Step 2. Keeping the head turned, lower the patient to the head-hanging position and hold for at least 30 s and until nystagmus disappears. Step 3. Without lifting



Vestibular migraine

- Treat with the drugs used for migraine prophylaxis. Controlled data are lacking.
- Antiemetics relieve symptoms during an attack.

Ménière's disease

- Refer to an otolaryngologist.
- Initial treatment is **diuretics and sodium restriction** (low-sodium diet 1000 mg/d).
- If attacks persist, give intratympanic glucocorticoid or gentamicin injections.
- Non-ablative surgery: decompression and shunting of the endolymphatic sac. Ablative surgery (vestibular nerve section, labyrinthectomy) is seldom required.

Central vertigo

- Treat as an emergency, with brain MRI and full neurological evaluation.
- Definitive therapy depends on the lesion (stroke, haemorrhage, demyelination, tumour).

Vestibular schwannoma

- MRI of the internal auditory canals confirms the diagnosis.

Bilateral vestibular hypofunction

- Refer for vestibular rehabilitation. **Do not use** vestibular suppressants, which increase imbalance.
- Look for ototoxic drugs (most commonly gentamicin or other aminoglycosides).
- An implanted vestibular prosthesis is a promising future option.

PPPD and functional dizziness

- Treat with SSRIs, cognitive-behavioural therapy and vestibular rehabilitation. Avoid vestibular suppressants.
- Benzodiazepines may attenuate psychosomatic dizziness and anxiety, but SSRIs are generally preferable.

Symptomatic drugs

- Use vestibular suppressants only for short-term control of active vertigo. Examples are the first few days of acute vestibular neuritis and acute attacks of Ménière's disease.
- They are less helpful in chronic dizziness and may hinder central compensation.

Table 3: Drugs for suppression of vertigo (usual oral starting dose in adults)

Drug	Class	Dose
Meclizine	Antihistamine	25–50 mg 3 times daily
Dimenhydrinate	Antihistamine	50 mg 1–2 times daily
Promethazine	Antihistamine	25 mg 2–3 times daily (also rectal, IM)
Diazepam	Benzodiazepine	2.5 mg 1–3 times daily
Clonazepam	Benzodiazepine	0.25 mg 1–3 times daily
Scopolamine	Anticholinergic	Transdermal patch (motion sickness only)

Table 24-2 — Harrison's 22e, pr.165. TABLE 24-2 Treatment of Vertigo

AGENT ^a	DOSE ^b
Antihistamines	
Meclizine	25–50 mg 3 times daily
Dimenhydrinate	50 mg 1–2 times daily
Promethazine	25 mg 2–3 times daily (also can be given rectally and IM)
Benzodiazepines	
Diazepam	2.5 mg 1–3 times daily
Clonazepam	0.25 mg 1–3 times daily
Anticholinergic	
Scopolamine transdermal ^c	Patch
Physical therapy	
Repositioning maneuvers ^d	
Vestibular rehabilitation	
Other	
Diuretics and/or low-sodium (1000 mg/d) diet ^e	
Antimigrainous drugs ^f	
Selective serotonin reuptake inhibitors ^g	

^aAll listed drugs are approved by the U.S. Food and Drug Administration, but most are not approved for the treatment of vertigo. ^bUsual oral (unless otherwise stated) starting dose in adults; a higher maintenance dose can be reached by a gradual increase. ^cFor motion sickness only. ^dFor benign paroxysmal positional vertigo. ^eFor Ménière's disease. ^fFor vestibular migraine. ^gFor persistent postural-perceptual vertigo and anxiety.

Vestibular rehabilitation

- It promotes central adaptation and compensation for vestibular loss.
- It may also help habituate motion sensitivity and perceptual dizziness.
- It uses graded exercises that progressively challenge gaze stabilisation and balance.

PEARLS

- Vertigo means acute asymmetry of vestibular input. Bilateral symmetric loss gives imbalance and oscillopsia, not vertigo.
- Timing is the best discriminator: seconds (BPPV, orthostatic hypotension), minutes (TIA), hours (Ménière's disease, vestibular migraine), days (neuritis, stroke).
- In acute prolonged vertigo, a normal head impulse test suggests a central cause, and an abnormal one suggests a peripheral lesion.
- Direction-changing, pure vertical or pure torsional nystagmus, or nystagmus not suppressed by fixation, indicates a central lesion.
- Unilateral hearing loss favours a peripheral cause. Diplopia, dysarthria and ataxia favour a central cause.
- Dix–Hallpike showing transient upbeat-torsional nystagmus confirms posterior canal BPPV. The treatment is the Epley manoeuvre, not drugs.
- Older patients with vascular risk factors and acute vestibular syndrome need stroke evaluation even if the examination looks peripheral.
- Limit vestibular suppressants to the first few days. Never use them in bilateral hypofunction or PPPD.
- Unexplained unilateral sensorineural hearing loss needs gadolinium MRI of the internal auditory canals.

17. Neurological findings that localise a lesion

ASKED 1* • Intermediate answer

Asked in: Oct 2024 P-I Q9(a) (5 marks)

Q: Neurological findings helpful in localizations of lesion in nervous system. [5]

SOURCE Harrison's 22e — Ch 26 Neurologic Causes of Weakness and Paralysis, §Prognosis, Pathogenesis, Distribution of Weakness — pp. 168–170
Harrison's 22e — Ch 433 Approach to the Patient with Neurologic Disease, §Coordination Examination, Gait Examination, Neurologic Diagnosis — p. 3382

Definition and principle

- Neurological localisation means interpreting history and examination to reach the **anatomic site** that best explains the findings. This comes before the aetiological diagnosis
- The sequence is: anatomic localisation → mode of onset and course → other medical data and laboratory findings → aetiological diagnosis
- Localisation narrows the differential diagnosis. It also guides which tests to select: electrolytes and blood counts, CSF, focused neuroimaging, or electrophysiology
- The examination may be normal even in serious disease such as seizures, chronic meningitis or TIA
- Uncommon presentations of common diseases are more likely than rare aetiologies

Level-wise localising findings



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