

DIAGNOSIS IN GENERAL PRACTICE

Test of time

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The test of time is not appropriate when “red flag” symptoms warrant immediate referral, but it can be helpful in patients presenting with common problems, such as diarrhoea (p 46), that have a known clinical course

What is it?

Patients often present to general practitioners with symptoms or signs that are ill defined and evolving, making it difficult to slot them neatly into a diagnostic category. In a cohort study of 500 patients presenting with common symptoms, 70% had improved at two weeks’ follow-up, and 60% of the remainder had improved at three months.¹ Making a precise diagnosis of all presenting problems is arguably not only unnecessary but also potentially damaging both to the patient and to the overall healthcare budget.²

General practice presents a good opportunity for using the test of time for diagnosis since arranging reassessment is relatively easy. Gray says that the general practice consultation should be seen as a total of 47 minutes spread over the course of a year, rather than a discrete 10 minute entity, allowing repeated evaluation in situations of diagnostic uncertainty.³

Diagnosis by test of time involves a careful initial assessment of the patient’s presenting problem(s), followed by one or more reassessment(s) after predefined period(s) of time. At the reassessment(s) the symptom or sign might have become more clearly defined, might have resolved, might be unchanged, or might have worsened, or additional signs or symptoms may have appeared. Diagnosis by time therefore relies on a good understanding of the course of condition(s) to enable appropriate reassessment(s). This article considers the test of time as a diagnostic method that is often used for defining the final diagnosis (figure).⁴

When can it be used?

In applying this diagnostic strategy it is important to distinguish those patients who require rapid investigation, treatment, or referral from those who would better be served by observation over a period. Test of time

should be used only in situations where the benefits of delay (lower risks of false positive diagnoses or avoiding unnecessary investigations) outweigh the harms of delayed or missed diagnoses. The test of time strategy can help to protect the patient from the harm of unnecessary investigations and the “cascade” effect of unexpected abnormal results generating further tests.⁵

The test of time is not appropriate when red flag symptoms warrant immediate referral, but it can be helpful in patients presenting with common problems, such as diarrhoea, where the initial assessment has not identified any red flags and the clinical course is reasonably well established for the commoner infectious causes. Some conditions in which the test of time is well accepted have limited published data on clinical course: in the management of an isolated enlarged lymph node, for example, current practice recommends waiting 4-6 weeks before arranging further specific investigations such as biopsy, providing there are no red flag symptoms or active infection.⁶

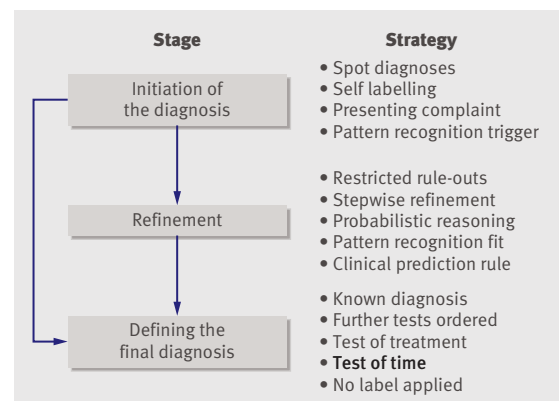
How does it go wrong?

Problems in the initial assessment

Inadequate assessment

The “safety net” of a follow-up appointment could tempt a clinician to undertake an inadequate initial assessment. This may result in poor definition of the presenting problem or any associated symptoms and a failure to identify red flags. Cancer presenting in the

This series aims to set out a diagnostic strategy and illustrate its application with a case. The series advisers are Kevin Barraclough, general practitioner, Painswick, and research fellow in community based medicine, University of Bristol; Paul Glasziou, professor of evidence based medicine, Department of Primary Health Care, University of Oxford; and Peter Rose, university lecturer, Department of Primary Health Care, University of Oxford.



Stages and strategies in arriving at a diagnosis

emergency department has been cited as a marker of inadequate initial assessment in primary care.⁷ Primary care clinicians should be aware of the challenge of assessment in the course of an illness, before more typical features have emerged. Another potential pitfall is a reluctance to measure vital signs that might help to distinguish, for example, between serious bacterial infection and viral illness.

Inappropriate discriminators

If we are going to observe patients over time then the baseline assessment must be based on discriminant information applicable to early symptoms or signs (and, ideally, also relevant to the setting and the patient spectrum). For example, the classic clinical features of meningococcal disease appear late in the illness; within the first four to six hours of the onset of meningococcal disease children have non-specific features such as fever, poor feeding, and irritability.⁸

Another example of an inappropriate discriminator is the “thunderclap” headache for subarachnoid haemorrhage. However, case series show that up to two thirds of patients with subarachnoid haemorrhage do not have an abrupt onset within seconds, but that the “worst headache of their lives” can evolve over several minutes.⁹ Consequently, many doctors incorrectly exclude the possibility of subarachnoid haemorrhage by considering that the absence of an abrupt “thunderclap” onset within seconds is a key discriminator.¹⁰

Many colorectal cancer guidelines focus on the symptom of rectal bleeding, but the most common initial presentation for this condition is a change in bowel habits.¹¹ The difficulty with using this symptom is that it has poor specificity and reliability.¹²

Problems in reassessment

Failed reassessment

The patient may not return, especially if the responsibility is placed solely on them. For example, in relation to cancer, Nylenna and Hjortdahl identified an important gap between doctors’ and patients’ understanding and interpretation of some key symptoms and signs: the doctors tended to recommend a quicker response rate for most of the symptoms and signs than did the patients.¹³

Biased reassessment

Especially when reassessing a subjective symptom or a physical sign, doctors will be influenced by earlier findings,^{14,15} and such bias could undermine the safety of the test of time diagnostic strategy. Clinicians should be aware of this and critically re-evaluate the working diagnosis if the condition does not follow the expected course. Patients’ recollections of their symptoms are often inconsistent,¹⁶ and an individual’s physical and psychological state (which may have changed since the initial assessment) can affect their assessment of the severity of a current symptom.¹⁷

Inability to determine important change

It can be difficult to establish whether a clinically important change has taken place if the course of the sign or symptom or the extent of any biological variability is uncertain—for example, diagnosis of hypertension may require repeated measurement of blood pressure over time.¹⁸ Problems can occur if the usual trajectory of the symptom or sign is not linear or if it has poor reliability,¹⁶ as is the case with change in bowel habit.¹²

Incorrect time frame

It is important to identify the clinical course of the problem diagnosed or suspected, since the time frame for reassessment is specific to the condition. For example, the time course for deterioration in meningitis (a matter of hours) is different from that for viral gastroenteritis, where dehydration can develop over days.

Narrow focus

In general practice, it is important to appreciate that diagnosis by time is not simply about the exclusion of serious physical illness but also the simultaneous consideration of medically unexplained symptoms and psychiatric disorders. Depression and anxiety often present with somatic symptoms that may resolve with prompt and effective treatment.¹⁹

How can we improve?

Careful initial assessment

Careful initial assessment should be a prerequisite for any test of time and must include information that can discriminate between possible diagnoses. The presenting problem, any associated symptoms or signs (especially red flags), comorbidities, and the patient’s current physical and emotional state must be clarified.¹⁷

Developing an explicit and comprehensive re-assessment plan

To minimise misunderstandings about reattendance, the follow-up plan must be explicit about reassessments, and this must be agreed with the patient. It should be based, as far as possible, on the known course of the presenting problem and the clinically important difference that needs to be detected.

From the patient’s perspective, a good test of time focuses on specific features or changes in the condition that suggest a need for reassessment, and a time frame during which the patient should observe these features before seeking reassessment (see box for examples).

Monitor progress with objective, reproducible measures

Wherever possible, monitoring by the general practitioner or practice nurse should use features that can be objectively assessed and that have good reproducibility. Examples include using dermatoscopy to photograph and measure skin lesions that do not warrant immediate removal, using a ruler or callipers to record the sizes of lymph nodes, using a tape measure for serial measurements of head circumference in

Time frames of common symptoms

Cough

Acute cough in children—50% recover within 5-10 days and 90% within 20-25 days^{23,24}

Children with pertussis positive serology—85% had cough two months after onset of symptoms, compared with 49% of those with negative serology²⁵

Sore throat

Sore throat (including *Streptococcus* positive) resolves in 40% by day 3 and in 85% by day 7²⁶

In serologically diagnosed Epstein-Barr virus infection, 74% have sore throat at diagnosis, 16% at 1 month, and 11% at 2 and 6 months²⁷

Conjunctivitis

By day 5, symptoms have resolved in 65% and by day 7, symptoms have resolved in 83% of patients^{28,29}

Diarrhoea

Infectious diarrhoea in adults and children—at 3 weeks, 76% no longer had symptoms³⁰

Diarrhoea lasted three or more days in 72% of children with *Campylobacter* infection and 22% with norovirus³¹

Back pain

Acute lower back pain (without sciatica)—at 6 weeks, 40% were completely pain free; at 12 weeks, 58% were pain free; at 1 year, 73% were pain free³²

Sciatica—at 2 years, 55% still had symptoms, and of those who recovered from sciatica, 61% still had lower back pain³³

Knee complaint

New episodes of pain and stiffness (excluding suspected fracture)—at 3 months symptoms persisted in 75% of patients and at 12 months symptoms persisted in 56%³⁴

children, and monitoring diarrhoea by assessing the frequency of stools.

When the patient is asked about changes in subjective symptoms, the options need to be balanced. For example, in dyspepsia, such options would be that the condition has improved, is unchanged, or has worsened.²⁰

Broaden the focus if necessary

After a test of time, another diagnostic strategy, such as the test of treatment, may be needed—for example, bronchodilators for cough that does not resolve.²¹ Frequent attendance with the same symptom over a period, combined with an inability to make sense of the presenting symptom, should alert us to avoid thinking solely about organic disease when attempting to make a diagnosis.²²

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DIAGNOSIS IN GENERAL PRACTICE

Acute diarrhoea in adults

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A common condition provides an example of the use of the test of time in diagnosis, explained in the accompanying article by Susanna Almond and Nick Summerton (p 43)

Case scenario

A 47 year old man consults because he has had diarrhoea for the past 10 days. Three weeks ago he travelled to Bangkok for an academic convention. He now has occasional cramping abdominal pain and feels generally off colour; he has not lost weight and has not noticed blood or mucus in his stools. He has taken loperamide for the past few days, without much benefit.

The diagnostic dilemma

The diagnostic dilemma is to distinguish between diarrhoea due to short term, probably infective, causes and diarrhoea that represents an early symptom of a more serious gastrointestinal disorder. Acute diarrhoea is somewhat arbitrarily defined as diarrhoea for less than four weeks.¹ It is said to affect almost every adult in the United Kingdom every year,² though most people do not consult a doctor about it.^{3,4} Viruses are the most common infectious cause in the community, and *Campylobacter* (12%) and rotavirus (8%) are the organisms most commonly isolated among people who consult a general practitioner,⁵ though isolation rates of norovirus have increased recently.⁶ Possible non-infective causes include drugs, alcohol, and anxiety as well as more serious problems such as inflammatory bowel disease and bowel cancer.

In distinguishing between self limiting and more serious causes of acute diarrhoea, the doctor needs to know the patient's background, including factors such as recent foreign travel; general health (comorbidities such as HIV infection, disorders such as hyperthyroidism and diabetes, and previous gastrointestinal surgery); "red flag" symptoms and signs, such as blood in the stool; recent hospital treatment or antibiotics; evidence of dehydration or intra-abdominal disease (a mass or marked abdominal tenderness, for example); and weight loss.

The diagnostic approach: the test of time

The investigation of acute diarrhoea in adults is a useful example of the test of time as a diagnostic approach in primary care.⁷ This approach is used in initial presentations of undifferentiated symptoms to discriminate

the minority of patients with serious disease, who require urgent attention, from the majority with self limiting or less serious problems. In a careful initial assessment, red flag symptoms for serious disease and more subtle discriminators pointing to a range of other diagnoses are excluded. This assessment is followed by one or more structured, planned reassessments, whose nature and timing are informed by knowledge of the epidemiology and course of the presenting symptoms.

Causes of acute diarrhoea

Many cases of acute diarrhoea resolve within two to four days⁸; different infective agents cause slightly different durations of symptoms. For example, diarrhoea due to rotavirus lasts three to eight days, norovirus a median of two days, and *Campylobacter* and *Salmonella* diarrhoea two to seven days.⁹ Diarrhoea lasting over a week is often associated with *Giardia*.¹⁰

Foreign travel and persistent symptoms raise the possibility of bacterial, viral, or protozoal infection, although in 25-50% of cases of "travellers' diarrhoea" no specific causative agent is identified.¹¹ Stool microscopy and culture for eggs and parasites are highly sensitive and specific,¹² and will identify infection with amoeba and *Giardia*, as well as other gut pathogens, including *Shigella*, *Salmonella*, *Yersinia*, *Campylobacter*, and pathogenic *Escherichia coli*. If symptoms persist after infective agents have been identified and treated, chronic gastrointestinal disorders is more likely, including irritable bowel syndrome, lactose intolerance, inflammatory bowel disease, coeliac disease, and colorectal cancer.

Red flags

Red flags may have a number of meanings in patients with acute diarrhoea. They may represent the alarm symptoms of an early presentation of a serious gastrointestinal problem such as inflammatory bowel disease or colorectal cancer (change in bowel habit, rectal bleeding, weight loss, systemic illness, etc); they may represent symptoms indicating serious systemic complications (sepsis, dehydration, abdominal disease), or they may be regarded as "discriminators"—symptoms that discriminate between self limiting diarrhoea and infective diarrhoea, for which investigation and appropriate treatment are required.

Discriminators

Duration of diarrhoea is important. Diarrhoea lasting for more than a week should lead to a decision to

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Learning points

- Acute diarrhoea (lasting less than four weeks) has a range of causes, most commonly short term and usually self limiting viral, bacterial, and protozoal infections, but it can herald chronic gastrointestinal conditions, including colorectal cancer, or can be due to underlying systemic illness, including endocrine disorders
- Use of the “test of time” in acute diarrhoea depends on knowing the epidemiology and course of the condition and provides a useful framework for management
- Prompt investigation to identify or exclude an infective cause is important, and assessment based on the patient’s age, clinical history, and presenting symptoms and signs (checking for “red flags”) may suggest further investigation, particularly if symptoms persist
- Acute diarrhoea has a low predictive value for inflammatory bowel disease and colorectal cancer, but persisting symptoms, particularly in older patients, merit prompt investigation
- Post-infective irritable bowel syndrome is common: 20% of irritable bowel syndrome patients attribute the onset of their condition to an infective episode

investigate, with the objective of identifying persistent infectious and non-infectious causes.¹⁰

Travel history may raise suspicion of exposure to more exotic organisms. As at least 50% of travellers returning from non-European destinations, particularly central America and South America and the Indian subcontinent, are likely to have a bacterial or parasitic cause for their diarrhoea,¹³ this group also merit investigation.

Blood in the stool may help in discriminating between non-self limiting infectious and non-infective colitis. Around 40% of patients with *Campylobacter* infection have blood in their stool (compared with 10% of those whose infections are due to other causes),⁸ and bloody stools are also common in infection with toxigenic *E coli*, *Salmonella*, *Shigella*, and *Yersinia*.¹⁰

Fever is present in around half of patients with infective diarrhoea, particularly in *Campylobacter* and rotavirus infections, compared with around 10% in non-infective diarrhoea.¹⁰

Headache seems to be most common in rotavirus infections,¹⁴ in which bloody stools are unusual, but it is a non-specific symptom and not a useful discriminator.

C reactive protein is more likely to be raised in gastroenteritis with a bacterial, rather than a viral, cause. It is of less value in diagnosing inflammatory bowel disease because its concentration is commonly below 10 mg/l in patients with ulcerative colitis but is raised in 75% of patients with Crohn’s disease.^{15,16}

High risk groups include older people and those with comorbidities, in whom the test of time should be applied with caution, and those with other important health problems, such as HIV infection and immunosuppression, who should be investigated at an early stage.

Problems with the test of time

Potential pitfalls in the use of the test of time include inadequate initial assessment, the use of inapplicable discriminators (such as the presence or characteristics of abdominal pain), and failure to reassess patients

adequately and objectively, according to Almond and Summerton.⁷ They point out the danger of inappropriate focus on a single organ system, which can lead to important physical or psychological disease being overlooked, and the danger of over-reliance on the accuracy of previous assessment made by others. In acute diarrhoea this translates into an emphasis on the importance of objective follow-up of progress or deterioration; being alert to the development of dehydration, sepsis, and systemic illness; and being aware of the possibility that the diarrhoea is related to a non-gastrointestinal disorder, such as hyperthyroidism or diabetes.

Case reassessment: non-infective causes of diarrhoea

In this patient, stool culture identified *Giardia lamblia*, which was treated with a course of metronidazole. Three weeks after treatment he returned as planned for reassessment, and still had diarrhoea, occasionally accompanied by cramping abdominal pain. Stool microscopy was now negative. With persistent symptoms, the likelihood of other gastrointestinal disorders is increased. The peak age for irritable bowel syndrome and inflammatory bowel disease is the third and fourth decades, and colorectal cancer is a possibility in a 47 year old man, so further investigations are needed to clarify the diagnosis.

A tissue transglutaminase antibody (tTgA) test for coeliac disease is appropriate in primary care.¹⁷ A xylose tolerance test can identify lactose intolerance secondary to *Giardia* infection. If inflammatory bowel disease or colorectal cancer are suspected, a haemoglobin estimation, along with erythrocyte sedimentation rate or C reactive protein, may support the diagnosis, but lower bowel endoscopy (preferably colonoscopy rather than flexible sigmoidoscopy, to ensure a full bowel examination) will be needed if diagnostic suspicion is high, particularly if there is a family history of colorectal cancer.

Case review

Because of concerns about a serious underlying cause for the diarrhoea, and although the predictive value of acute diarrhoea for a diagnosis of inflammatory bowel disease or colorectal cancer is low,¹⁸ these investigations, including colonoscopy, were performed over the next three weeks. All had negative results, but the diarrhoea persisted. There was no suggestion of laxative misuse (a surprisingly common cause of persistent “factitious” diarrhoea^{19,20}) or evidence of an underlying endocrine abnormality.

This patient’s acute diarrhoea almost certainly came from an infection picked up while overseas; although *Giardia* was eradicated, symptoms persisted. Thorough investigation excluded non-malignant causes of persistent diarrhoea, such as coeliac disease, lactose intolerance, endocrine disorders, inflammatory bowel disease, and colorectal cancer. The final diagnosis was post-infective irritable bowel syndrome.

Almost one in five patients with irritable bowel syndrome (particularly those with *Campylobacter* and *Shigella* infection) date the onset of symptoms to an episode of diarrhoea or acute gastroenteritis.²¹ This patient's management proceeded on the basis of a clear explanation, an honest appraisal of prognosis, and the use of anti-diarrhoeal agents and occasional anti-spasmodics, with good effect.

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From our archive

The plague of the East (1894)

The Chinese readily ascribe the outbreak of plague to the absence of rain causing an impure water supply and a more than usually insanitary condition of houses and drains. The heavy rains that fell in May and June tended in nowise to lessen the prevalence of the disease when it was fully established. This may be partly explained by the fact that for the season of the year the temperature was abnormally low, whereas a high temperature seems antagonistic to the pestilence. Again, during wet weather Chinese are confined to their houses, and so more within the area of contagion.

In Yunnan, according to Mr. Rocher, pigs, goats, rats, and other animals die in great numbers before man is affected. In Canton rats were the only animals observed to suffer; an exceptional mortality was observed amongst them two or three weeks before cases of plague were noted, and this sequence of events persisted throughout the epidemic. A high mortality amongst rats in a district of the city quite free from sickness was most surely followed by an outbreak of plague, so much so that people came to regard these rodents as heralds of the coming evil, and when possible hastened removal to safer quarters. They would come out of their holes in broad daylight, run and tumble about in the streets in an aimless and dazed

manner, and die. Certain officials took steps to have these dead animals collected, and from the quarter near the south gate over 22,000 dead rats were said to have been removed and buried in pits outside the walls...

Although, as concerns man, all classes suffered from the plague, certain conditions of life seemed to confer immunity: First, the greater number of those attacked were women and children, especially female children, that is, those living most indoors; secondly, those living upstairs escaped the disease much more readily than those living on the ground floor; thirdly, the boating population, consisting of about 250,000 people, who live and sleep on the water, enjoyed almost complete immunity, so much so that many well-to-do people observing this circumstance made a temporary home on the river.

The Plague in the East. *BMJ* 1894;2:615-6, doi:10.1136/bmj.2.1759.615

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