

The last century of symptom-oriented research in emergency presentations – have we made any progress?

Roland Bingisser, Christian Hans Nickel

Emergency Department, University Hospital, Basel, Switzerland

Summary

This review is dedicated to the last century of symptom-oriented research, taking three symptom complexes as typical examples of medical progress, and focusing on emergency presentations. Landmark publications in each area are discussed, with an attempt to focus on the methods used to achieve major breakthroughs.

In abdominal pain, progress was achieved over a century ago by correlating symptoms and surgical pathology. Most diagnoses were made by using the clinical tools elaborated with careful observation and clinical examination. Together with the later reported outcomes, surgeons had an early and powerful tool for symptom-oriented research.

In dyspnoea, progress was achieved much later, as a universal definition had to be elaborated over decades by consolidating clinical research, predominantly symptom-pathology correlation, and experimental research, such as function testing and experiments with animals and humans. In nonspecific presentations in emergency situations, progress has been achieved only recently, most probably owing to the fact that elderly patients are presenting in steeply increasing numbers, and the hallmark of disease presentation in the elderly seems to be less specific symptoms and complaints. This may be caused by altered physiology, polymorbidity, polypharmacy and the multiple difficulties encountered when taking histories in the elderly.

Taken together, symptom-oriented research has been an important contributor to medical progress in the last century. Though it may be challenged by image- and laboratory-oriented research, it will remain part of patient-centred research because the epidemiology of symptoms, their clinical outcomes and their diagnostic importance according to severity will be the basis for the diagnostic process.

Key words: nonspecific disease presentation, symptom-oriented research, dyspnea, abdominal pain, elderly, geriatric emergency

An abbreviated history of symptom-oriented research

Although at the end of the 19th century symptom-oriented research was the engine driving advances in medical science, it was suffering from deficient funding and a lack of visibility at the end of the 20th century. Because insufficient investment in symptom-oriented research was sensed, the National Institutes of Health (NIH) started a grant programme for pain, nausea and dyspnoea research, and the US Congress announced the “decade of pain research” at the start of the 21st century [1].

Medicine has changed since Hippocrates and Galen founded symptom-oriented research, and their prime goal – doing what is best for the individual patient [2] – has evolved into the concept of doing what is best for a large number of patients, “evidence-based medicine”, by use of modern research methods and statistics [3, 4].

Observation of symptoms and evolving disease was a key component of slow, but definite progress (see table 1 below) until the late 19th century, when new technologies, such as bacterial cultures on the aqueous humour of an ox’s eye allowing proof of the “germ theory” of infectious disease [5], and led to a series of medical revolutions. Together with other breakthrough technologies at the turn of the 20th century, such as the detection of X-rays [6], new insights into the human body were achievable, and surgery of the abdominal organs was now state-of-the art in an emergency presentation of, for example, abdominal pain [7].

The approach to symptom-oriented research in the early 20th century was different from now, but the results were surprisingly similar. Publications were numerous, and a textbook editor of 1917 complained of “the overflow of publications in medical journals” [8]. Articles were generally authored by a single male investigator who described his personal experience, rated signs and symptoms subjectively, and added case reports to make his point [9, 10]. They emphasised observation and clinical examination, the differential diagnosis, and indications for, for example, abdominal surgery, which were similar to those of the present day, as exemplified in comprehensive textbooks [8, 11].

In this review, three very different complexes of symptoms, exemplifying the respective methods used for research in

each complaint, will be highlighted, with a focus on emergency presentations.

Although *nonspecific complaints* have drawn attention only recently [12], *abdominal pain* has led the way due to the symptom-pathology correlation in surgically treated patients that was recognised at the beginning of the 20th century [9], when the fastest advances in symptom-oriented research were made in this area. Thirty years later, immense pathophysiological challenges had to be faced before *acute dyspnoea* could be associated with the regulatory mechanisms of respiration and underlying diseases [13], and up to the 1960s no consensus was reached as to the universal definition of this complaint [14].

Symptoms, complaints and symptom-oriented research: in need of definitions

Symptoms may be established as medically legitimate where they can be isolated conceptually and, where possible, their parameters defined and displayed tangibly. Thus defined, symptoms may be targeted for treatment or, where treatment is not available, attention given to the activities of daily life they are seen to affect. Thus, symptoms are understood in terms of problems located within the individual [15].

Symptoms are initially presented by patients in narrative form, and can therefore be called “complaints”. Only when semistructured interviewing was introduced by Louis [16] (see also table 1), were symptoms systematically assessed. In this review, we therefore prefer the term “complaints” when referring to the patient’s own perception.

The essential steps in the diagnostic process are the analysis of symptoms, clinical examination and clinical reasoning. This review is about the first step, as the analysis of symptoms is known to be the most important contributor to the diagnostic process [17–19]. Symptom-oriented research is based on the problems or complaints presented by the patients. It is therefore problem-oriented. It is diagnosis- or differential-diagnosis-centred, the methods usually being observational.

The importance of symptom-oriented research is shown by the importance of the diagnostic process. Irrespective of the approach chosen – (a) hypothetico-deductive, involving several steps of problem definition and hypothesis genera-

tion, (b) pattern recognition, involving a mental library of signs and symptoms, or (c) scheme-inductive reasoning, involving an organised structure of knowledge usually in the form of inductive trees [20] – the recognition and interpretation of symptoms remains the first and crucial step in analytical medicine [21].

Furthermore, the epidemiology of symptoms is the basis for the determination of any pretest probability, health outcomes according to symptoms are of importance in emergency situations and severity assessments of symptoms may aid physicians in decision making.

In table 1, different approaches to symptom-oriented research are shown. Outcomes could be determined only by autopsy before the 19th century, but heavily relied on clinical diagnoses in the last century. Advances in statistical methodology were important for improvements, but the assessment of symptoms has also changed: Although histories were reported as the original narrative of the patients until the 19th century, structuring was important to improve discrimination, and finally “descriptors” were predefined in order to optimise standardisation, the latest invention being verbal autopsies, in which machine-learning was shown to be superior to physicians in certain experiments for the first time in medical history [22].

Specific and nonspecific complaints in emergency presentations

Though never exactly defined, the concept of specific presentations or complaints encompasses the idea that cer-

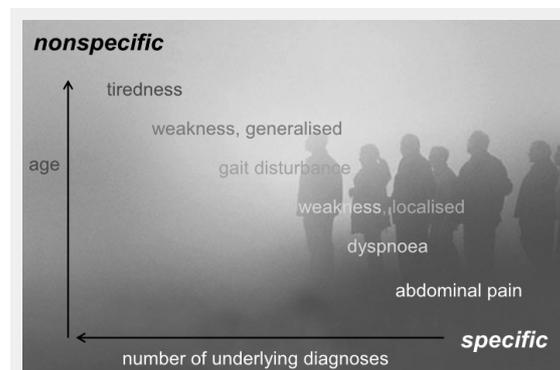


Figure 1 Specific and nonspecific presenting symptoms.

Table 1: Approaches to symptom-oriented research.

Researcher	Method	Outcome	Statistical method
Hippocrates (500 BC) [2]	Observation of symptoms	Mortality	Descriptive
Morgagni (1761) [117]	History of symptoms, unstructured	Autopsy results	Comparative (old cases in the literature)
Laennec (1819) [118]	Signs and symptoms Auscultation	Pathological anatomy	Validation (clinical examination)
Louis (1834) [16]	History of symptoms, structured	Autopsy	Correlation
Elliot (1991) [88]	Questionnaire, predefined “descriptors”	Clinical diagnosis	Cluster analysis
Wang (2005) [119]	Data extraction, 22 original articles	Clinical diagnosis	Meta-analysis (pooled sensitivities, likelihood ratios)
Flaxman (2011) [22]	Verbal autopsy Analysis	Clinical diagnosis	Random Forest method (machine learning)

tain symptoms are more or less “specific” to a small group of diseases; for example, dyspnoea presenting as an emergency is quite specific for severe pulmonary and cardiac diseases such as obstructive and infiltrative lung disease, pulmonary embolism and oedema, as well as myocardial infarction or heart failure [23, 24]. Most probably, over 90% of all emergency presentations with severe dyspnoea will be diagnosed within this group. Severe dyspnoea needing immediate acute care is so specific for these conditions that it can be readily differentiated using simple ultrasound protocols [24].

In acute abdominal pain, appendicitis, cholecystitis, perforated ulcers, diverticulitis and ileus may account for 90% of diagnoses made postoperatively. In children, over 90% of acute abdominal pain is caused by appendicitis and nonspecific pain [25], whereas in patients under 50 years of age, four underlying diagnoses, and in patients over 50 years of age, seven diagnoses, account for >80% of all presentations with “acute abdomen” [26]. Therefore, acute abdominal pain and dyspnoea are typical examples of “specific complaints” (figure 1).

In the last century, symptom-oriented research focused on a relatively small number of these specific complaints. Textbooks of medicine and surgery have no more than two dozen chapters on presenting symptoms, if they are symptom-oriented at all [27, 28]. On the other hand, it is perfectly clear that patients’ complaints extend over a much broader spectrum, may well be multiple and complex, and often do not fit into the relatively narrow concept of specific complaints. Though naturally limited, the concept of specific complaints has boosted advances in medicine for over a century. The limitation to a small number of specific symptoms, however, seems to be a recent phenomenon, considering the 2500-year history of symptom-oriented research. It can be hypothesised that the breakthrough in technology at the end of the 19th century has contributed to this development, because textbooks published before the detection of mycobacteria are much more detailed in the description of a variety of symptoms and their assumed origin [5]. Powell, for example, aimed at delineating the connection between the morbid anatomy and the clinical symptoms, and proposed six different diagnoses (alveolar phthisis, catarrhal pneumonia, fibroid phthisis, haemorrhagic phthisis, recurrent phthisis, and tubercular phthisis) for a condition later to be known as tuberculosis [29]. It can be concluded that a century ago there was less focus on the small set of specific symptoms driving symptom-oriented research today – a much broader variety of complaints and symptoms was acknowledged as the important basis of the diagnostic process in medicine. Up to the 1970s, symptomatology was more widely accepted as a diagnostic and research basis [30], but has ever since lost ground. Though focusing on a reduced set of symptoms has contributed to the success of modern medicine, it is obvious that certain presentations may have been underestimated and, boosted by the fact that a nonspecific presentation is often a hallmark of disease in the elderly [31], were found to be of importance only recently when geriatric (emergency) medicine emerged [32–34].

In contrast to specific complaints, nonspecific complaints may be defined as all complaints that are not part of the set

of specific complaints, because an active definition would require an almost endless enumeration of possible symptoms and complaints [34]. Typical examples are generalised weakness [35], non-injurious falls [36], gait disturbance [37] and tiredness [38].

These complaints have not been described in the text books of the last century’s and are still largely disregarded today, although various cohorts have shown prevalence between 5% and 21% [39, 40] in emergency populations in Europe [40]. Therefore, nonspecific complaints were chosen as an example of a late breakthrough, possibly because of a revival of symptom-oriented research at the end of the 20th century.

Taken together, abdominal pain, dyspnoea and nonspecific complaints are selected for their high prevalence in emergency presentations [34], as well as for the fact that for each complaint the advances were made using the typical and successful methods of the respective decades when breakthroughs were achieved (surgery for abdominal complaints, physiological tests for dyspnoea, and prospective cohorts for nonspecific complaints).

Abdominal pain with emergency presentation: leader in symptom-oriented research

Scientific knowledge has to be concentrated to the extreme – more than 400 reviews and 5000 articles under the title of “abdominal pain” have been published. However, only one practice guideline [41] for acute care physicians is retrievable, which suggests a certain lack of interest by the scientific community as compared with diagnosis-oriented guidelines, which are abundant.

At the end of the 19th century, symptom-oriented research [42] was, next to technology [6], the main driver of progress in medicine. The importance and influence of surgery around 1900 can hardly be overestimated and is demonstrated by a quote of Maylard in 1910: “previously, it was only through the accidental light thrown upon the subject by a necropsy that a certain symptom during life received its correct explanation after death...” [43]. To exemplify the state-of-the-art in abdominal pain, cases discussed over a century ago shed light on the differential indication for surgery. One argument was that “...the longer the symptoms have persisted the more uncertain is the effect of operative treatment ...; operations, on the other hand, performed within a reasonable time of the onset of the symptoms are ... always immediately successful” [7]. At the onset of the 20th century, the symptomatology was well known to surgeons: complaints, symptoms and physical signs were adequately described and weighed against each other, with emphasis on the nature of the pain, the rigidity of the abdominal wall, the facial expression of the patient, fever, pulse and vomiting [9].

In the 1920s, when antibacterial agents were not available (except for arsenic compounds used against syphilis) mortality rates of 4% to 7% were reported for complicated cases of the two most common emergency presentations of acute abdominal pain, namely appendicitis and cholecystitis [44].

This relatively low mortality demonstrates that physicians and surgeons had incorporated the knowledge gained from symptom-oriented research at the incipient 20th century. Most relevant details of the patient history and physical examination for the major pathologies were known at the time. Clinical signs and symptoms of peptic ulcers, peritonitis, pancreatitis, appendicitis, cholecystitis, enteritis and ileus were described in detail in textbooks [8, 45], and surgeons published cases of rare entities, such as mesenteric vein thrombosis [9], that they had unsuccessfully operated on.

Still, a few presenting complaints turned out not to be specific, such as “classical ulcer-type postprandial symptoms” [46] that, by today’s knowledge, do not help to discriminate between functional dyspepsia and peptic ulcer [47]. However, a history of prompt and good symptomatic relief by a course of proton-pump inhibitors suggests an acid-related disorder [48].

What other progress have we made in the last hundred years in diagnosing abdominal pain? Although dyspepsia was similarly defined in 1917 [8], “new entities” emerged: the “irritable bowel syndrome” was a term first used in the 1950ies, whereas “nonulcer dyspepsia” appears to have come into vogue in the 1940s [49, 50] after case-series in which patients with typical ulcer symptoms were confirmed not to have a peptic ulcer crater. In 1943 Edwards and Copeman studied 436 patients using barium X-ray; 50% had no evidence of structural disease despite dyspeptic symptoms, arguably owing to the mediocre diagnostic accuracy of the diagnostic method chosen [49].

The condition now called “nonspecific abdominal pain” has become the most frequent “entity” for abdominal emergency presentations in patients younger than 50 years of age. It was first described in the 1970s [51], was also called “undiagnosed abdominal pain treated in hospital” [52] and showed an excellent prognosis in long-term follow-up [53]. An overlap of chronic abdominal pain, irritable bowel syndrome and nonspecific abdominal pain was later apparent – these entities seem more prevalent in younger females [54] and lower income classes [55], but no underlying anatomical pathology has been found. In past decades, research interest in functional bowel disease was enormous; certain publications were cited over a thousand times [56].

Surprisingly, only for the last decades was evidence produced that symptoms may vary widely depending on sex and age of the patient. The first systematic review on emergency presentation of abdominal pain in the elderly was published in 1994 and included approximately 42,000 patients [57]. De Dombal concluded that acute abdominal pain in the elderly patient presents a significant and challenging problem because diagnostic accuracy is lower, and mortality far higher, than in younger patients [57].

It has since become evident that emergency presentations of elderly patients with abdominal pain may greatly differ from presentations in younger patients. Elderly patients often present later in the course of disease and they have more nonspecific complaints. At the same time, a broader differential diagnosis has to be considered. A high number of comorbidities, polypharmacy, altered mental status and failure of care facilities to communicate the reason for transfer have been proposed as explanations for these dif-

ficulties [33, 34, 57]. These findings are not exclusive to abdominal pain, and will be discussed in the section about nonspecific presentation.

Still, it seems surprising that these facts materialised only, considering that for over a century great clinicians have made important contributions by meticulously observing patients and correlating their observations with the final diagnoses and pathologies. One of these clinicians was William Osler, who mastered narrow descriptions and concise characterisations of different types of abdominal pain. Upon reading this following account [58] – “... pain in the splenic region, tenderness on pressure and slight swelling of the organ. On several occasions I have heard a well-marked peritoneal friction rub...” – most physicians in later centuries would diagnose splenic infarction.

Taken together, in the area of *abdominal pain presenting as emergency*, the major advances in research were made at the beginning of the 20th century owing to the widespread use of abdominal surgery. Though technology has greatly improved since, morbidity and mortality have not dramatically changed, if patients in similar conditions are compared [44, 59]. In the last fifty years, break-through findings using the methodology of symptom-oriented research were rare with the exception of functional bowel disorders [60], and publications therefore focused on special populations, such as the pregnant [61], paediatric [62] and geriatric [57].

Dyspnoea with emergency presentation: the prolonged search for a definition

Going back to the 19th century, dyspnoea was depicted as a rather nonspecific complaint: “the number of diseased states capable of giving rise to dyspnoea is so great, and of such various and even opposite kinds, that not even the first step can be taken towards assessing the value of dyspnoea in any given case” [63]. However, the comparison of two common conditions, cardiac dyspnoea and asthmatic dyspnoea, in the same publication shows that observation of typical patients was the prime tool of symptom-oriented research in the 19th century. The ongoing controversy about bronchitis being a precursor of asthma was started in 1868, and the differential diagnosis of pulmonary oedema, asthma and emphysema was broadly discussed at that time [63].

As for abdominal pain, the literature of the incipient 20th century is full of case reports describing most of the common and many of the rare illnesses, but there was no attempt to perform prospective observational studies or experiments in order to understand the nature of dyspnoea and the pathophysiology of breathing; taking emphysema as an example, neither aetiology [64] nor pathophysiology [65] was really comprehended in the 1920s. A major role was attributed to humidity, and Switzerland was cited as a country where the incidence of emphysema was low due to dry and cold air [66].

Between the world-wars, two hypotheses were proposed to explain hypercapnia in emphysema: Scott [65] suggested that impaired ventilation is the result of chemical factors that influence the respiratory drive; Christie [67] proposed

that ventilatory insufficiency is primarily the result of abnormal respiratory mechanics, and that the respiratory muscles are unable to perform the necessary work to provide adequate ventilation. These hypotheses, which were generated from observation of symptomatic patients, were later proven to be imprecise or wrong [68], but the methods, such as cardiac [69] and pulmonary function testing [70], used to correlate symptoms with physiology had to be refined first [71].

In the 1920s, several novelties need to be noted: the time of all-male science was over [72], inter-observer differences were acknowledged as a fact when taking a patient's history, and experiments were now agreed to associate symptom and function [72]. It was also increasingly clear that acute dyspnoea was quite a specific complaint, as the majority of underlying conditions were now attributed to the heart, lungs and kidneys [73]. Furthermore, it was recognised that cardiac dyspnoea occurred in two different forms: the nightly paroxysms [73] of congestive heart failure, in severe forms associated with Cheyne-Stokes type respiration [74], and as an accompanying or presenting symptom in myocardial infarction [75].

In the 1930s, Conner may have been the first to publish an observational study on "coronary thrombosis" with a complete outcome for over 200 cases. Furthermore, he realised that the presentation was dependent on gender, and that dyspnoea was one of the features of myocardial infarction [75]. Due to a lack of immediate publication, the first (self-)catheterisation in 1929 [76] was not repeated until the 1940s, when Courmand and Richards used the Fick principle to measure cardiac output and showed in hundreds of subjects that the procedure was safe [77].

In the 1940s and 1950s, pulmonary and cardiac pathophysiology [78, 79] was explored using newer methods such as plethysmography [78] and cardiac catheterisation [76, 77]. However, the definition of dyspnoea ("dyspnoea occurs whenever the individual's actual ventilation cannot easily be provided by his breathing capacity") given by Richards and Courmand in 1941 [80] was still similar to Means' and Meakins' in the 1920s [81, 82] and very mechanistic, omitting, for example, the fact of psychogenic hyperventilation. Richards believed in symptom-oriented research and quoted Conner in a lecture on dyspnoea: "...new advances should support and add to our simpler forms of knowledge, rather than replace them; ... in the analysis and treatment of disease, laboratory findings, whatever their nature, should be our servants and not our masters" [83]. This picture of the "true clinician" who was convinced that symptom-orientation should always lead the way, in daily practice and in research, would soon fade, as technology advanced.

In the 1950s, symptom-oriented research had definitely moved from a case-report and single author based approach to a cross-sectional, multi-observer and group-oriented approach, incorporating Cochrane's landmark paper on interobserver variability [3], but there was still no universal definition of dyspnoea. Wright commenced his 1954 publication with the words "dyspnoea has no generally accepted meaning in the scientific literature" [84].

One of the first conferences on dyspnoea in 1966 attempted to gather all information from the different specialties in-

involved in dyspnoea research [85]. In the 1980s, the respiratory drive was investigated in depth and dyspnoea was experimentally correlated with certain external stimuli [86]. In 1990, it was finally acknowledged that there is no unique peripheral site that mediates dyspnoea. Rather, receptors in the airways, diaphragm, and intercostal muscles, as well as the sense of respiratory effort, can all be involved [87]. The term "breathlessness" was reintroduced in order to discriminate the different sensations a volunteer or a patient can experience when challenged [88]. After a century of research it was time to go back to the roots and ask physicians for more clinical differentiation in patients suffering from dyspnoea. Unfortunately, the distinguishable sensations were not very specific to a single cause, and not many clinicians have heard about the language of dyspnoea [87, 89].

About 20 years ago, standardised diagnostic protocols were introduced and ever since, standards, pathways and algorithms have been published for work-up in the office [90, 91], in the emergency department [92] and even when giving advice by telephone [90].

Taken together, the fastest advances in research on dyspnoea were made in the middle of the 20th century owing to the incorporation of the findings by physiologists into clinical practice. While multiple causes underlie dyspnoea in a general population, it has turned out to be a specific symptom in an emergency presentation, as the bulk of the underlying disease is cardiorespiratory. For further reading see table 2.

Nonspecific complaints with emergency presentation: still in search of a definition

Generalised weakness, repeated noninjurious falls and functional impairment are typical complaints in an elderly population [31]. According to different cohorts, their prevalence in emergency presentations is up to 21% [40], and patients under 65 years are contributing to this increasingly recognised type of presentation [40]. The literature on nonspecific symptoms is scarce, possibly owing to a missing universal definition. Considering that this task has taken decades in specific complaints, the scientific discussion certainly needs more original data to be able to agree on a general definition of nonspecific complaints. The first publications on patients presenting with *weakness*, *functional impairment* or *dizziness* appeared in the late 1980s and 1990s [31, 32]. They described a geriatric population, without focusing on emergency presentations, but were not able to trigger symptom-oriented research in this area. Over a decade later, the first articles on the nonspecific type of presentation in emergency settings were published and demonstrated that in 42% of all presentations an underlying condition was found in the emergency department (ED) [40]. This was confirmed by a later study showing that 50% of older individuals without specific complaints suffered from an acute medical problem [12]. The population presenting with nonspecific complaints turned out to be a particularly high-risk group for adverse outcomes (e.g. functional decline, dependence and death) [93].

In the 1990s it was recognised that functional impairment was mostly caused by muscle weakness, and multiple studies measuring muscle function were published [94]. However, the distinction between the “frail elderly” and the “elderly with acute functional impairment” was not made until recently, when it became apparent that frailty is a geriatric syndrome needing assessment with the prerequisite of a stable situation and an adequate setting – all of which are lacking in acute care [95–98].

Generalised weakness is one of the most frequent presenting symptoms in emergency presentations [39]. In a recent report, it was responsible for 13% of all nontrauma admissions and was the single most frequent presenting symptom in this group, being caused by serious disease in the majority of cases [34]. This contrasts with the common assumption that nonspecific symptoms, such as weakness, tend to be benign.

Physicians in acute care settings face a significant challenge when evaluating patients with nonspecific symptoms, owing to the broad spectrum of underlying disease. The diagnostic work-up is usually time-consuming and the possibility of acute morbidity such as pneumonia [99–104] is high. With increasing age, acute illness tends to present in a nonspecific manner [100–104]. It has been reported that even myocardial infarction can present with overwhelming weakness [105]. The clinical presentation of infection in the elderly, as another example, is often atypical or nonspecific and might even appear to be unrelated to the underlying condition [33, 106]. In elderly patients, the typical manifestations of infection, fever and leucocytosis may be absent or blunted in up to 30% of serious infections [107]. It is a well-accepted fact that elderly patients may present with atypical symptoms of urinary tract infection such as weakness and subtle mental status changes. In fact,

Table 2: Interesting reading on dyspnoea research.

Finding/highlight	Field of interest	Year	Publication
Noxious vapours exhaled by lung	Cardiovascular/pulmonary	204	Galen [120]
Oxygen needed for combustion	Pulmonary/metabolic	1775	Lavoisier [121]
Periodic breathing	Cardiac	1818	Cheyne [122]
Dyspnoea and haemoptysis	Cardiovascular/embolism	1870	Johnson [123]
Cheyne-Stokes and CO ₂	Cerebral	1908	Pembrey [124]
pH and dyspnoea	Metabolic	1913	Henderson [125]
Cardiac dyspnoea and lung function	Cardiac	1916	Peabody [126]
Definition of dyspnoea	Cardiac and pulmonary	1929	Means [82]
Dyspnoea as angina equivalent	Cardiac	1930	Conner [75]
Pulmonary insufficiency	Pulmonary	1941	Courmand [80]
Dyspnoea and cough rating	Epidemiology/statistics	1951	Cochrane [3]
Lung stretch and dyspnoea	Pulmonary	1954	Wright [84]
Definition of dyspnoea	Cardiac and pulmonary	1966	Howell [85]
Diagnostic approach	Cardiac and pulmonary	1989	Pratter [127]
Chemosensitivity in dyspnoea	Pulmonary/asthma	1994	Kikuchi [128]
Telephone triage in dyspnoea	Cardiac and pulmonary	2003	Zoorob [90]
Cerebral activation and dyspnoea	Cerebral	2009	Leupoldt [129]

Table 3: Current attempts to describe or define nonspecific complaints.

Nomenclature	Setting	Definition/description
Home care impossible [12]	ED	(1) When primary care or referring physicians explicitly noted on referral note that home care services and/or social and familial support were not able to support the patient at home anymore. (2) When the triage nurse could not identify any specific chief complaint except insufficient social, familial and/or nursing support.
Nonspecific complaints [34]	ED	All complaints that are not part of the set of specific complaints or signs, or where an initial working diagnosis cannot be definitively established. Prerequisite are vital signs within normal limits and a triage level indicating the need of more than 1 external resource
Unexplained symptoms [130]	GP	Those complaints for which a general practitioner, after clarifying the reason for encounter, taking history and performing physical examination, is unable to establish a diagnosis
General disability [39]	ED	A conscious patient's own (or referring institution's) experience of rapid decline of physical and/or mental condition but no signs or symptoms from a specific organ and no knowledge of ongoing fever. Corresponding ICD-codes: R69, R41.0, R63.0, R63.4, R64, R69
Atypical symptoms and nonspecific functional decline [33]	General medicine university hospital, almost all admitted from ED	Atypical symptoms were defined as six syndromes (delirium, falls, immobility, incontinence, functional decline and breakdown of social supports) with the following criteria: Delirium was defined by the criteria of DSM-III-R.11. Falls were unintentional displacement to the ground occurring within 1 week before admission. Immobility was loss of ability to ambulate or transfer within 1 week before admission. Incontinence was a new onset of the inability to control urination or defecation within 1 week before admission. Nonspecific functional decline was a change in the ability to perform personal activities of daily living and/or instrumental activities of daily living within 1 week before admission. A breakdown in social supports was the inability of the premorbid supports to continue to provide adequate care for that patient.
Frailty [36]	Community-dwelling older adults	Frailty was defined as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 lbs in past year), self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity
No cardinal symptom [131]	ED	None of these symptoms: Chest pain, abdominal pain, dyspnoea, headache.

ED = Emergency Department; GP = general practitioner

delirium and functional decline may be the first signs of bacteraemia in the elderly. Such “nonurinary” symptoms are more likely to occur in patients with comorbidities and/or dehydration [108]. Similarly, more than half of patients older than 70 years can have nonrespiratory symptoms as the presenting complaint for pneumonia, and over a third have no systemic signs of infection [109]. Furthermore, physiological changes and pharmacological factors may limit changes in vital signs in response to an acute disease such as pneumonia, limiting the ability of clinicians to rely on vital sign abnormalities to identify serious illness in the elderly [110].

Even after two decades of research, defining symptoms such as “not feeling well”, “feeling weak”, “being tired”, remains a challenge, but has been attempted in different ways (table 3). A framework has recently been proposed, including a working definition [34]: “all symptoms that are not part of the set of specific symptoms can be called non-specific”, as it has been shown that multiple diagnoses are responsible for this type of presentation. Even a fair-to-moderate pretest probability would have to include over a dozen entities in as many diagnostic groups. This “negative definition” has a major advantage: there is no “endless” list of complaints defining the presentation. The disadvantage is the extremely broad case-mix. Therefore, it remains to be shown that “nonspecific” is a presentation with common underlying diseases and outcomes, irrespective of the type of complaint, such as “not feeling well”, “feeling weak”, “being tired” or “feeling dizzy”. To come forward with a universally accepted definition is a prerequisite for the management of the patient by the use of diagnostic protocols. These have been developed for a number of presenting chief complaints, such as acute chest pain, dyspnoea, or flank pain [34, 92], where the pretest probabilities in all conditions are known, and where management strategies have been tested [111–113]. Unfortunately, in nonspecific complaints uncertainty often accompanies the diagnostic process, which results in ineffective or suboptimal triage of these patients, delayed ED throughput, and inadequate patient disposition [34, 114]. These factors may contribute to the reported unfavourable outcomes [115, 116]. Next to a universal definition, risk stratification tools are needed to efficiently manage patients with nonspecific complaints.

Conclusion

Symptom-oriented research needs to be reinforced – not only because it has been among the major drivers of scientific medicine in the last century and before, but also because the clinical features of disease (i.e. complaints, history and clinical examination) often provide noteworthy information that cannot be replaced by imaging and laboratory testing. Additionally, a thorough assessment of symptoms is low-cost and high-value, considering the continuous shortening of physician-patient interactions, and could lead to elimination of superfluous testing. Symptom-oriented research is also of importance for the epidemiology of symptoms and their pathophysiology. Health outcomes, such as quality of life and mortality, need to be known on the basis of symptoms, as a sound diagnosis is not always available in emergency situations.

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Correspondence: Roland Bingisser, MD, Department of Emergency Medicine, University Hospital Basel, Petersgraben 2, CH-4031 Basel, Switzerland, [Roland.Bingisser\[at\]usb.ch](mailto:Roland.Bingisser[at]usb.ch)

References

- Boswell MV, Giordano J. Reflection, analysis and change: the decade of pain control and research and its lessons for the future of pain management. *Pain Physician*. 2009;12:923–8.
- Srinivasan M. From the Editors' Desk: Hippocrates and Patient-centered Medicine. *J Gen Intern Med*. 2011;27(2):135.
- Cochrane AL, Chapman PJ, Oldham PD. Observers' errors in taking medical histories. *Lancet*. 1951;1:1007–9.
- Perrier A. Evidence-based medicine and critical care. *Schweiz Med Wochenschr*. 1999;129:1572–82.
- Brown L. Robert Koch. *Bull N Y Acad Med*. 1932;8:558–84.
- Rontgen WC. On a New Kind of Rays. *Science*. 1896;3:227–31.
- Pritchard E. Two Cases of Obscure Abdominal Pain: Operations: Results. *BMJ*. 1902;2:1944–6.
- Dornblüth O. Kompendium der Inneren Medizin. In: March 1917 ed. Leipzig: Verlag von Veit & Comp.; 1917:1–688.
- Thomas JL. The Causes of Acute Abdominal Pain in the Healthy, Exclusive of Traumatism. *BMJ*. 1903;2:186–8.
- Thomas CP. The Significance and Treatment of Abdominal Pain. *Cal State J Med*. 1911;9:330–4.
- Warren JC. The international text-book of surgery. 1 ed. Philadelphia: Saunders; 1902.
- Rutschmann OT, Chevalley T, Zumwald C, Luthy C, Vermeulen B, Sarasin FP. Pitfalls in the emergency department triage of frail elderly patients without specific complaints. *Swiss Med Wkly*. 2005;135:145–50.
- Richards DW, Cournand A, Rappaport I. Relation of the Regulatory Mechanism of Respiration to Clinical Dyspnea. *Proceedings of the National Academy of Sciences of the United States of America*. 1935;21:498–501.
- Campbell EJ, Howell JB. The sensation of breathlessness. *BMJ*. 1963;19:36–40.
- Monks J. Experiencing symptoms in chronic illness: fatigue in multiple sclerosis. *International Disability Studies*. 1989;11:78–83.
- Louis P. An Essay on Clinical Instruction. S Highley, 1834. Cited by Reiser SJ. *Medicine and the reign of technology*. Cambridge University Press; 1981.
- Hampton JR, Harrison MJ, Mitchell JR, Prichard JS, Seymour C. Relative contributions of history-taking, physical examination, and laboratory investigation to diagnosis and management of medical outpatients. *BMJ*. 1975;2:486–9.
- Eskelinen M, Lipponen P. Usefulness of history-taking in non-specific abdominal pain: a prospective study of 1333 patients with acute abdominal pain in Finland. *In vivo*. 2012;26:335–9.
- Gruppen LD, Woolliscroft JO, Wolf FM. The contribution of different components of the clinical encounter in generating and eliminating diagnostic hypotheses. *Research in medical education: proceedings of the annual Conference Conference on Research in Medical Education*. 1988;27:242–7.
- Coderre S, Mandin H, Harasym PH, Fick GH. Diagnostic reasoning strategies and diagnostic success. *Medical education*. 2003;37:695–703.
- Riley I. Computer-based analysis of verbal autopsies: revolution or evolution? *Population health metrics*. 2011;9:26.
- Flaxman AD, Vahdatpour A, Green S, James SL, Murray CJ, Population Health Metrics Research C. Random forests for verbal autopsy ana-

- lysis: multisite validation study using clinical diagnostic gold standards. *Population health metrics*. 2011;9:29.
- 23 Ray P, Birolleau S, Lefort Y, et al. Acute respiratory failure in the elderly: etiology, emergency diagnosis and prognosis. *Critical care*. 2006;10:R82.
- 24 Lichtenstein DA, Meziere GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest*. 2008;134:117–25.
- 25 Dickson JA, Jones A, Telfer S, de Dombal FT. Acute abdominal pain in children. *Scand J Gastroenterol Suppl*. 1988;144:43–6.
- 26 Telfer S, Fenyo G, Holt PR, de Dombal FT. Acute abdominal pain in patients over 50 years of age. *Scand J Gastroenterol Suppl*. 1988;144:47–50.
- 27 Sabiston DC, Townsend CM. *Sabiston textbook of surgery: the biological basis of modern surgical practice*. 19th ed. Philadelphia, PA: Elsevier Saunders; 2012.
- 28 Fortin AH, Smith RC. *Smith's patient-centered interviewing: an evidence-based method*. 3rd ed. New York: McGraw-Hill Professional; 2012.
- 29 Bishop PJ. Powell and Hartley' – a Famous Textbook on Diseases of the Chest, 1872–1921. *Tubercle* 1965;46:91–101.
- 30 de Dombal FT, Horrocks JC, Staniland JR, Guillou PJ. Construction and uses of a "data-base" of clinical information concerning 600 patients with acute abdominal pain. *Proceedings of the Royal Society of Medicine*. 1971;64:978.
- 31 Chew WM, Birnbaumer DM. Evaluation of the elderly patient with weakness: an evidence based approach. *Emerg Med Clin North Am*. 1999;17:265–78.
- 32 Gordon M. Differential diagnosis of weakness – a common geriatric symptom. *Geriatrics*. 1986;41:75–80.
- 33 Jarrett PG, Rockwood K, Carver D, Stolee P, Cosway S. Illness presentation in elderly patients. *Arch Intern Med*. 1995;155:1060–4.
- 34 Nemeč M, Koller MT, Nickel CH, et al. Patients presenting to the emergency department with non-specific complaints: the Basel Non-specific Complaints (BANC) study. *Academic emergency medicine: official journal of the Society for Academic Emergency Medicine* 2010;17:284–92.
- 35 Nickel CH, Nemeč M, Bingisser R. Weakness as presenting symptom in the emergency department. *Swiss Med Wkly*. 2009;139:271–2.
- 36 Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *The journals of gerontology Series A, Biological sciences and medical sciences* 2001;56:M146–56.
- 37 Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of sub-clinical cardiovascular disease with frailty. *The journals of gerontology Series A, Biological sciences and medical sciences* 2001;56:M158–66.
- 38 Avlund K, Schultz-Larsen K, Davidsen M. Tiredness in daily activities at age 70 as a predictor of mortality during the next 10 years. *J Clin Epidemiol*. 1998;51:323–33.
- 39 Safwenberg U, Terent A, Lind L. The Emergency Department presenting complaint as predictor of in-hospital fatality. *European journal of emergency medicine: official journal of the European Society for Emergency Medicine*. 2007;14:324–31.
- 40 Vanpee D, Swine C, Vandenbossche P, Gillet JB. Epidemiological profile of geriatric patients admitted to the emergency department of a university hospital localized in a rural area. *European Journal of Emergency Medicine: official journal of the European Society for Emergency Medicine*. 2001;8:301–4.
- 41 Clinical policy for the initial approach to patients presenting with a chief complaint of nontraumatic acute abdominal pain. *American College of Emergency Physicians. Ann Emerg Med*. 1994;23:906–22.
- 42 Allfrey CH. South-Eastern Branch: Fifty Years of Medical and Surgical Progress and the Part Played in It by Experimental Research. *BMJ*. 1910;2:127–9.
- 43 Maylard AE. An Address On Reflex Pain In Diseases Of The Abdominal Viscera: Delivered before the Greenock and District Faculty of Medicine. *BMJ*. 1910;1:616–21.
- 44 McNeill Love RJ, Lond MS. Hunterian Lecture on the treatment of some acute abdominal disorders. *Lancet*. 1929:375–81.
- 45 Aird WC. Discovery of the cardiovascular system: from Galen to William Harvey. *Journal of Thrombosis and Haemostasis*. 2011;9(Suppl 1):118–29.
- 46 Jennings D, Richardson JE. Giant lesser-curve gastric ulcers. *Lancet*. 1954;267:343–50.
- 47 Tominaga K, Higuchi K, Iketani T, et al. Comparison of gastrointestinal symptoms and psychological factors of functional dyspepsia to peptic ulcer or panic disorder patients. *Inflammopharmacology*. 2007;15:84–9.
- 48 Orlando RC. Why is the high grade inhibition of gastric acid secretion afforded by proton pump inhibitors often required for healing of reflux esophagitis? An epithelial perspective. *Am J Gastroenterol*. 1996;91:1692–6.
- 49 Edwards H, Copeman WS. Dyspepsia: An Investigation. *BMJ*. 1943;2:640–2.
- 50 Friedman MH. Peptic ulcer and functional dyspepsia in the armed forces. *Gastroenterology*. 1948;10:586–606.
- 51 Ferguson IL. Laparoscopy for the diagnosis of nonspecific lower abdominal pain. *Br J Clin Pract*. 1974;28:163–5.
- 52 Rang EH, Fairbairn AS, Acheson ED. An enquiry into the incidence and prognosis of undiagnosed abdominal pain treated in hospital. *British Journal of Preventive & Social Medicine*. 1970;24:47–51.
- 53 Jess P, Bjerregaard B, Brynitz S, et al. Prognosis of acute nonspecific abdominal pain. A prospective study. *Am J Surg*. 1982;144:338–40.
- 54 Buddingh KT, Wieselmann E, Heineman E, Broens PM. Constipation and nonspecific abdominal pain in teenage girls referred for emergency surgical consultation. *J Pediatr Gastroenterol Nutr*. 2012;54:672–6.
- 55 Magni G, Rossi MR, Rigatti-Luchini S, Merskey H. Chronic abdominal pain and depression. Epidemiologic findings in the United States. *Hispanic Health and Nutrition Examination Survey. Pain*. 1992;49:77–85.
- 56 Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci*. 1993;38:1569–80.
- 57 de Dombal FT. Acute abdominal pain in the elderly. *J Clin Gastroenterol*. 1994;19:331–5.
- 58 Lawrence YR, Pokroy R, Berlowitz D, Aharoni D, Hain D, Breuer GS. Splenic infarction: an update on William Osler's observations. *The Israel Medical Association journal: IMAJ*. 2010;12:362–5.
- 59 Tiwari MM, Reynoso JF, Tsang AW, Oleynikov D. Comparison of outcomes of laparoscopic and open appendectomy in management of uncomplicated and complicated appendicitis. *Ann Surg*. 2011;254:927–32.
- 60 Wang A, Liao X, Xiong L, et al. The clinical overlap between functional dyspepsia and irritable bowel syndrome based on Rome III criteria. *BMC gastroenterology*. 2008;8:43.
- 61 Lazarus E, Mayo-Smith WW, Maimiero MB, Spencer PK. CT in the evaluation of nontraumatic abdominal pain in pregnant women. *Radiology*. 2007;244:784–90.
- 62 Brown EL, Brown DF, Nadel ES. Pediatric abdominal pain. *J Emerg Med*. 2009;36:72–5.
- 63 Salter H. Remarks on the Diagnosis of Dyspnoea. *BMJ*. 1868;2:587–9.
- 64 West S. On chronic bronchitis and emphysema as the result of acute pneumonia. *Lancet*. 1910;2:1413–.
- 65 Scott RW. Observations on the pathologic physiology of chronic pulmonary emphysema. *Arch Intern Med*, 1920;26:544–60.
- 66 Barr J. An Address On Some Observations On Bronchitis And Emphysema: Delivered before the English Division of the Border Counties Branch of the British Medical Association. *BMJ*. 1908;1:909–14.
- 67 Christie RV. The Elastic Properties of the Emphysematous Lung and Their Clinical Significance. *J Clin Invest*. 1934;13:295–321.
- 68 Roussos C, Koutsoukou A. Respiratory failure. *Eur Respir J Suppl*. 2003;47:3s–14s.
- 69 Cournand A, Bryan NA, Richards DW. Cardiac Output in Relation to Unilateral Pneumothorax in Man. *J Clin Invest*. 1935;14:181–9.
- 70 Cournand A, Baldwin ED, Darling RC, Richards DW. Studies on Intrapulmonary Mixture of Gases. Iv. The Significance of the Pulmonary

- Emptying Rate and a Simplified Open Circuit Measurement of Residual Air. *J Clin Invest.* 1941;20:681–9.
- 71 Gaensler EA. Air velocity index; a numerical expression of the functionally effective portion of ventilation. *Am Rev Tuberc.* 1950;62:17–28.
- 72 Hewlett AW, Lewis JK, Franklin A. The Effect Of Some Pathological Conditions Upon Dyspnea During Exercise: I. Artificial Stenosis. *J Clin Invest.* 1925;1:483–95.
- 73 Adams RD. Nocturnal Dyspnea: Special Reference to its Treatment with Thyroid. *Transactions of the American Climatological and Clinical Association American Climatological and Clinical Association.* 1922;38:213–20.
- 74 Pitt GN, Pembrey MS, Allen RW. Observations upon Cheyne-Stokes' Respiration. *Med Chir Trans.* 1907;90:49–82 15.
- 75 Conner LA, Holt E. The subsequent course and prognosis in coronary thrombosis: An Analysis of 287 Cases. *Am Heart J.* 1930;5:705–19.
- 76 Bolt W, Forssmann W, Rink H. Technic and practical significance of cardiac catheterization for functional diagnosis and therapy of cardiac and pulmonary diseases. *Medizinische Klinik.* 1953;48:1614–20.
- 77 Courmand A, Riley RL, Breed ES, et al. Measurement of Cardiac Output in Man Using the Technique of Catheterization of the Right Auricle or Ventricle. *J Clin Invest.* 1945;24:106–16.
- 78 Blumenthal W. The significance of plethysmography for the study of respiratory function. *Zeitschrift für die gesamte innere Medizin und ihre Grenzgebiete* 1954;9:125–8.
- 79 Nyboer J. Electrical impedance plethysmography; a physical and physiologic approach to peripheral vascular study. *Circulation.* 1950;2:811–21.
- 80 Cournand A, Richards DF. Pulmonary insufficiency. Discussion of a physiological classification and presentation of tests. *Am RevTuberc.* 1941;44:26.
- 81 Meakins J. A British Medical Association Lecture on – The cause and significance of dyspnoea in pulmonary disease. *BMJ.* 1924;1924:613–7.
- 82 Means JH. Dyspnoea. *Medicine.* 1929;3:309–416.
- 83 Richards DW, Jr. The Lewis A. Conner memorial lecture, the nature of cardiac and of pulmonary dyspnea. *Circulation.* 1953;7:15–29.
- 84 Wright GW, Branscomb BV. The origin of the sensations of dyspnea. *Transactions of the American Clinical and Climatological Association.* 1954;66:116–25.
- 85 Howell JBL, Campbell EJM, University of Manchester., Boehringer Ingelheim Ltd. Breathlessness; proceedings of an international symposium held on 7 and 8 April 1965 under the auspices of the University of Manchester. Philadelphia.; F.A. Davis Co.; 1966.
- 86 Castele RJ, Connors AF, Altose MD. Effects of changes in CO₂ partial pressure on the sensation of respiratory drive. *J Appl Physiol.* 1985;59:1747–51.
- 87 Simon PM, Schwartzstein RM, Weiss JW, Fencl V, Teghtsoonian M, Weinberger SE. Distinguishable types of dyspnea in patients with shortness of breath. *Am Rev Respir Dis.* 1990;142:1009–14.
- 88 Elliott MW, Adams L, Cockcroft A, MacRae KD, Murphy K, Guz A. The language of breathlessness. Use of verbal descriptors by patients with cardiopulmonary disease. *Am Rev Respir Dis.* 1991;144:826–32.
- 89 Mahler DA, Harver A, Lentine T, Scott JA, Beck K, Schwartzstein RM. Descriptors of breathlessness in cardiorespiratory diseases. *Am J Respir Crit Care Med.* 1996;154:1357–63.
- 90 Zoorob RJ, Campbell JS. Acute dyspnea in the office. *Am Fam Physician.* 2003;68:1803–10.
- 91 Morgan WC, Hodge HL. Diagnostic evaluation of dyspnea. *Am Fam Physician.* 1998;57:711–6.
- 92 Bingisser R. Emergency Standards [Internet]. [Cited 2012 Dec 12]. Available from: <http://www.emergencystandards.com>.
- 93 McCusker J, Verdon J, Tousignant P, de Courval LP, Dendukuri N, Belzile E. Rapid emergency department intervention for older people reduces risk of functional decline: results of a multicenter randomized trial. *J Am Geriatr Soc.* 2001;49:1272–81.
- 94 Dayhoff NE, Suhrheinrich J, Wigglesworth J, Topp R, Moore S. Balance and muscle strength as predictors of frailty among older adults. *J Gerontol Nurs.* 1998;24:18–27; quiz 54–5.
- 95 Hastings SN, Purser JL, Johnson KS, Sloane RJ, Whitson HE. Frailty predicts some but not all adverse outcomes in older adults discharged from the emergency department. *J Am Geriatr Soc.* 2008;56:1651–7.
- 96 Puts MT, Monette J, Girre V, et al. Does frailty predict hospitalization, emergency department visits, and visits to the general practitioner in older newly-diagnosed cancer patients? Results of a prospective pilot study. *Crit Rev Oncol Hematol.* 2010;76:142–51.
- 97 Au A, Puts MT, Fletcher JD, Sourial N, Bergman H. Frailty markers predicting emergency department visits in a community-dwelling sample of vulnerable seniors in Montreal. *Canadian Journal on Aging = La Revue Canadienne du Vieillissement* 2011;30:647–55.
- 98 Goldstein JP, Andrew MK, Travers A. Frailty in Older Adults Using Pre-hospital Care and the Emergency Department: A Narrative Review. *Canadian Geriatrics Journal.* 2012;15:16–22.
- 99 Nemeč M, Koller MT, Nickel CH, et al. Patients presenting to the emergency department with non-specific complaints: the Basel Non-specific Complaints (BANC) study. *Academic emergency medicine: official journal of the Society for Academic Emergency Medicine.* 2010;17:284–92.
- 100 Gordon M. Differential diagnosis of weakness – a common geriatric symptom. *Geriatrics.* 1986;41:75–80.
- 101 Samaras N, Chevalley T, Samaras D, Gold G. Older patients in the emergency department: a review. *Ann Emerg Med.* 2010;56:261–9.
- 102 Chew WM, Birnbaumer DM. Evaluation of the elderly patient with weakness: an evidence based approach. *Emerg Med Clin North Am.* 1999;17:265–78.
- 103 Peters M-L. The older adult in the emergency department: aging and atypical illness presentation. *Journal of emergency nursing: JEN: official publication of the Emergency Department Nurses Association.* 2010;36:29–34.
- 104 Rutschmann OT, Chevalley T, Zumwald C, Luthy C, Vermeulen B, Sarasin FP. Pitfalls in the emergency department triage of frail elderly patients without specific complaints. *Swiss Med Wkly.* 2005;135:145–50.
- 105 Bean WB. Masquerades of myocardial infarction. *Lancet.* 1977;1:1044–6.
- 106 Henschke PJ. Infections in the elderly. *Med J Aust.* 1993;158:830–4.
- 107 Norman DC, Yoshikawa TT. Fever in the elderly. *Infectious disease clinics of North America* 1996;10:93–9.
- 108 Ginde AA, Rhee SH, Katz ED. Predictors of outcome in geriatric patients with urinary tract infections. *J Emerg Med.* 2004;27:101–8.
- 109 Venkatesan P, Gladman J, Macfarlane JT, et al. A hospital study of community acquired pneumonia in the elderly. *Thorax.* 1990;45:254–8.
- 110 Lim WS, Macfarlane JT. Defining prognostic factors in the elderly with community acquired pneumonia: a case controlled study of patients aged > or = 75 yrs. *The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology.* 2001;17:200–5.
- 111 Russi EW, Leuenberger P, Brandli O, et al. Management of chronic obstructive pulmonary disease: the Swiss guidelines. *Official Guidelines of the Swiss Respiratory Society. Swiss Med Wkly.* 2002;132:67–78.
- 112 Verdon F, Herzig L, Burnand B, et al. Chest pain in daily practice: occurrence, causes and management. *Swiss Med Wkly.* 2008;138:340–7.
- 113 Rossetti AO, Novy J, Ruffieux C, et al. Management and prognosis of status epilepticus according to hospital setting: a prospective study. *Swiss Med Wkly.* 2009;139:719–23.
- 114 Grossmann FF, Zumbund T, Frauchiger A, Delport K, Bingisser R, Nickel CH. At risk of undertriage? Testing the performance and accuracy of the emergency severity index in older emergency department patients. *Ann Emerg Med.* 2012;60:317–25 e3.
- 115 Nickel CH, Ruedinger J, Misch F, et al. Copeptin and peroxiredoxin-4 independently predict mortality in patients with nonspecific complaints presenting to the emergency department. *Academic emergency medicine: official journal of the Society for Academic Emergency Medicine.* 2011;18:851–9.

- 116 Ruedinger JM, Nickel CH, Maile S, Bodmer M, Kressig RW, Bingisser R. Diuretic use, RAAS blockade and morbidity in elderly patients presenting to the Emergency Department with non-specific complaints. *Swiss Med Wkly.* 2012;142:w13568.
- 117 Morgagni J. *The Seats and Causes of Diseases Investigated by Anatomy* New York. Translated by Benjamin Alexandar, 1769 Facsimile. With a preface, introduction, and a new translation of five letters by Paul Klemperer; 1960.
- 118 Laennec R. *A Treatise on the Diseases of the Chest.* Translation by John Forbes of the 1st French edition. London: Underwood, 1821. (Reprinted by MacMillan (Hafner Press). New York, 1962.) Cited by Reiser SJ. *Medicine and the reign of technology.* Cambridge University Press 1981.
- 119 Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA.* 2005;294:1944–56.
- 120 Galen, Furlley DJ, Wilkie JS. *Galen on respiration and the arteries.* Princeton, N.J.: Princeton University Press; 1984.
- 121 Lavoisier LA. *Mémoire sur la nature du Principe qui se combine avec les Métaux pendant leur calcination et qui en augmente le poids.* *Mémoires de l'Académie Royale des Sciences.* 1775;1778:520–6.
- 122 Cheyne J. A case of apoplexy in which the fleshy part of the heart was converted into fat. *Dublin Hosp Rep.* 1818;2:216–23.
- 123 Johnson G. A Lecture on Haemoptysis: Its Causes, Results, and Treatment. *BMJ.* 1870;1:149–51.
- 124 Pembrey MS. Observations on Cheyne-Stokes respiration. *J Pathol Bacteriol.* 1908;12:258–U65.
- 125 Henderson LJ. *The Regulation of Neutrality in the Animal Body.* Science. 1913;37:389–95.
- 126 Peabody FW. Some factors in the production of cardiac dyspnea. *J Amer Med Assoc.* 1916;67:1136–8.
- 127 Pratter MR, Curley FJ, Dubois J, Irwin RS. Cause and evaluation of chronic dyspnea in a pulmonary disease clinic. *Arch Intern Med.* 1989;149:2277–82.
- 128 Kikuchi Y, Okabe S, Tamura G, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Engl J Med.* 1994;330:1329–34.
- 129 von Leupoldt A, Sommer T, Kegat S, et al. Down-regulation of insular cortex responses to dyspnea and pain in asthma. *Am J Respir Crit Care Med.* 2009;180:232–8.
- 130 van Bokhoven MA, Koch H, van der Weijden T, Grol RP, Bindels PJ, Dinant GJ. Blood test ordering for unexplained complaints in general practice: the VAMPIRE randomised clinical trial protocol. [ISRCTN55755886]. *BMC family practice.* 2006;7:20.
- 131 Mockel M, Searle J, Muller R, et al. Chief complaints in medical emergencies: do they relate to underlying disease and outcome? The Charite Emergency Medicine Study (CHARITEM). *European Journal of Emergency Medicine: official journal of the European Society for Emergency Medicine* 2012.

Figures (large format)

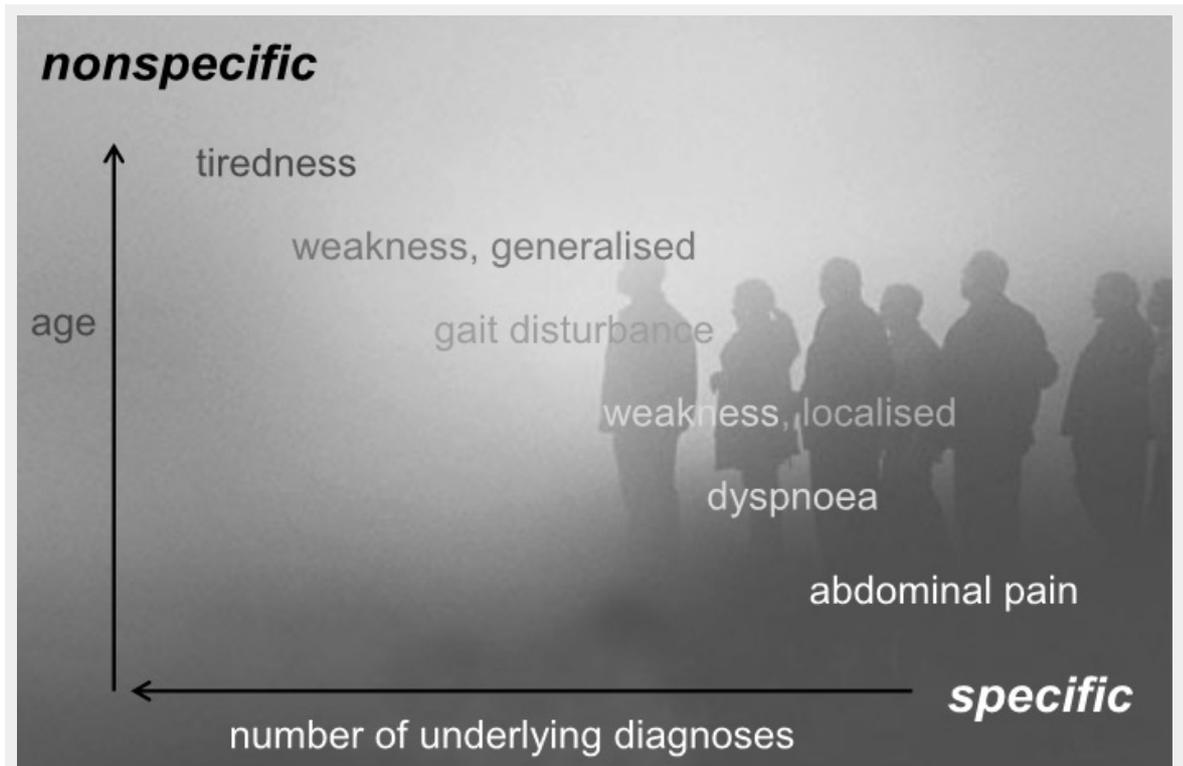


Figure 1
Specific and nonspecific presenting symptoms.