
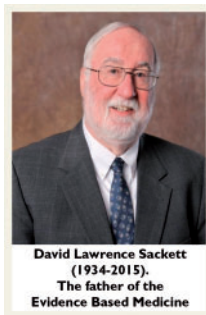
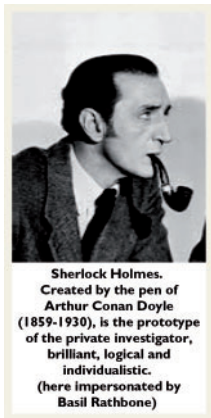


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# The impossible interviews—Sherlock Holmes interviews David Sackett: ‘how much can we trust the guidelines?’

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## Medicine before and after the era of guidelines

SH: I was eager to meet the father of Evidence Based Medicine and of the guidelines. So, today, I am delighted to do this interview as the ‘Guideline culture’ you created has gradually spread since the 1990s and, progressively, it is now influencing the activities of virtually all scientific societies. In the past, when I was interested in medicine (*at the time I was inspired by Dr Joseph Bell, professor of surgery at Edinburgh Medical School*) medicine was the ‘art of intuition’ and ‘smart intelligence’. The great medical practitioners of the past relied simply on their own personal intuition based on their interaction with the patient and the disease. Today doctors have evidence-based medicine and guidelines to direct them. Sometimes, I wonder whether this has been a positive step forward or a step backwards in the history of medical culture.

DS: Thanks and . . . I am honoured! The worth of a man is judged by the worth of his opponents and I couldn’t ask for more! Evidence Based Medicine consists in the conscious, judicious, and explicit use of the best evidence available to make decisions about the care of individual patients.<sup>1</sup> Previously, despite some exceptions, medicine was anecdotal and not based on objective data. Physicians relied on the non-critically validated opinions of authorities in the field as well as on their personal judgement or instinct. The new evidence-based culture is a

response to the deregulated, self-referential climate of those days. The new scientific approach has generated an avalanche of randomized controlled clinical trials, to provide robust, objective data, which must be carefully ‘sifted’ and interpreted by the experts.

## Guidelines and evidence-based medicine, facts, and myths

SH: I did expect your considerations. So I documented myself in every way and, theoretically, you are right but, allow me to ask you whether you are referring to facts or myths. For example, I notice that, if we consider as a whole the major cardiovascular guidelines published between 1984 and 2008 (53 official documents, totalling 7196 recommendations), only 11% of the recommendations had level evidence A (i.e. were generated by prospective randomized clinical trials) while 48% had a level C of evidence (i.e. based on non-unanimous expert opinion).<sup>2</sup> If I am not mistaken, this means that almost 50% of the recommendations relied simply on expert opinion. Not very different from the past, or so it seems! Moreover, after the initial phase of enthusiastic welcome of new guidelines, criticisms often tend to emerge:

- Clinical trials do not come into being spontaneously or by some divine will—in most cases, they are the fruit of a convergence of interest between a leading research group and pharmaceutical or biomedical companies. Often, the companies nominate (and pay) the so-called ‘leaders’, and this could bias the ‘objectivity’ of the research.
- Hence, behind the guidelines there are economic incentives. The risk is that, by accepting such incentives, non-impartial users could act to cut healthcare costs at the expense of treatment.
- There is another risk—that the choice of guidelines’ authors may not be on scientific merit or appropriateness, but based on political criteria, e.g. selected by scientific societies for reasons of geographical representativeness or political expediency.

DS: I see you have done some investigation but, in my opinion, the points you make are merely details! Your ‘accusations’ reveal your bias and hostility towards official institutions. The fact is that the guidelines of the major national and international scientific societies provide a periodical update and summary of the available literature. This makes

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them an extremely useful clinical tool that it would be difficult, if not impossible, for the single physician to construct. In cardiovascular medicine, both registries and dedicated observational studies have shown a clear benefit in terms of reduced mortality and morbidity following application of the guidelines, particularly regarding the treatment of heart failure, atrial fibrillation and acute coronary syndromes. These are facts!<sup>3-7</sup>

As for independence from drug and device companies, you cannot ignore the recent institution of Evidence Review Committees (ERCs)<sup>8</sup> providing independent systematic review and analysis of data relevant to key clinical questions

You also have to acknowledge the effort that has been made in recent years to change the focus of guidelines from procedure-centric to condition-centric. Thus, procedures such as pacemakers, defibrillators and cardiac resynchronization, which were previously addressed in guidelines on device-based therapies, are now addressed in guidelines on bradycardia and cardiac conduction delays, ventricular arrhythmias and sudden cardiac death, syncope, and heart failure.<sup>8</sup> This represents a real shift for the better.

## Diagnostic component vs. therapeutic component of guidelines

SH: All right, I can agree that some of the topics you mentioned can apply to treatment, but what about guidelines for diagnosis? It is very difficult to force the diagnostic process of a disease into a series of practical behavioural recommendations. To me, the diagnostic act itself has a 'creative' and 'intuitive' component that is difficult to describe by numbers or by fixed steps. This is especially true for the first of the two moments of diagnosis, i.e. 'suspicion'. Even though my investigative method is frequently described as 'deductive' (*from the general to the particular*) or 'inductive' (*from particular to general*), in reality, it is an 'abductive' process. To use the words of the philosopher C S Peirce 'Abduction is the process of forming an explanatory hypothesis'. Actually, induction establishes a rule, whilst deduction merely develops the necessary consequences of a given hypothesis. Only 'abduction' leads to a new hypothesis (*that of course has to be confirmed*). Good detectives and good clinicians share the same underlying approach as scientific researchers (*Karl Popper's hypothetic-deductive model*).<sup>9</sup>

DS: good point, I must admit! I agree that there is an initial moment of abductive reasoning required, which is closely linked to individual intuition and experience. Following on its heels, however, there must be an orderly process of selecting which instrumental and laboratory tests can best lead one to the definitive diagnosis, and this process has to be evidence-validated.

## Didactic impact of guidelines

SH: Let's move onto another, more general issue. Guidelines, in my opinion, should also play a didactic role but, actually, they often have the opposite effect on medical trainees and, more generally, on anyone wishing to consolidate their culture and experience. While guidelines do, offer a unique tool to summarize the available literature, at the

**Table 1** Pros and cons of the clinical guidelines

### Six good reasons why we should not follow guidelines

1. They focus on the disease rather than on the patient.
2. Their recommendations are based more often on expert opinions than on solid EBM.
3. They usually refer to studies conducted on relatively young patients with a low comorbidity burden.
4. They deter individual reasoning and suppress the deductive element of diagnostic decision-making in the individual patient.
5. They attenuate scientific curiosity and the motivation for further research by shifting attention from what we (still) don't know to what we know (consolidated evidence).
6. They are the product of a 'lobby' of authors, often with strong links with pharmaceutical or biomedical companies.

### Six good reasons why we should use the guidelines

1. They are an exceptional tool summarizing the latest published research.
2. They provide a useful 'checklist' of possible treatments to consider in the individual patient.
3. They explain the general rationale behind each diagnosis.
4. They outline the principles and steps for making diagnostic and therapeutic decisions.
5. They promote a more rational use of economic resources.
6. They provide a convenient line of defense in the event of malpractice charges.

same time they tend to restrict one's autonomy in interpreting pathophysiological and clinical signs and, in general, they regiment the whole clinical approach.

DS: I see what you mean but, please, don't forget that a clear methodological premise is present at the front of guidelines, with the intent to contextualize the interpretation (*i.e. referring to the specific patient setting*). Furthermore, you don't take into consideration the continuous evolution of clinical practice guidelines from an editorial and graphical point of view.<sup>8</sup> I would have liked to write a single summary document with the great SH, but I'm afraid it's not possible. If you agree, together we could list the reasons for and against the widespread dissemination of clinical guidelines in medicine (*Table 1*).<sup>10</sup>

SH: Excellent!

DS: At the end of this interview I would like to attract your attention and to know your opinion on a specific case, the GL for heart failure with reduced ejection fraction (HFrEF) which many consider already obsolete. After 15 years of silence, five landmark RCTs are now available and four new classes of drugs have been developed in less than 6 years: angiotensin receptor/neprilysin inhibitor (ARNi), sodium-glucose co-transporters 2 inhibitors (SGLT2i), soluble guanylate cyclase (sGC) modulators and myosin activators, needs to be incorporated in the actual GL.

SH: I do agree. I have spent my 'investigatory life' searching for every dissonant element or inconsistency in the scene of crimes. Allow me to tell you, the discrepancies already existing in the present GL and the potential clashes between old rules and the new achievements.

The pillars of the actual EBM based treatments of HFrEF are drugs that, with the exception of ivabradine, are all aimed at antagonizing the neuroendocrine activation. So, the proposed 'step approach' on one hand was logical to achieve the best possible neutralization of the negative effects of an excess of neuroendocrine activation. But, on the other hand scaling the next step in case of persistence of symptoms or awaiting to reach the target dose established in RCT (*which usually never tested other smaller doses*) results in a waste of precious time for the patients.<sup>11,12</sup> This algorithm needs to be changed as:

- Three of the studied class of agents are really new. They do not antagonize the neuroendocrine activation, but target additional and different pathways not intercepted by the conventional therapy
- The fourth class of the new drugs, the ARNI, acutally and paradoxically increase instead of decrease a specific and beneficial neuroendocrine system, that of atrial natriuretic peptides
- The so called target doses of standard drugs are often only slightly more effective in comparison with starting doses and consistent benefits in outcomes are already reached at low doses.
- If physicians prioritize the achievement of target doses of each class of drug before starting new treatments, it takes several months to prescribe all recommended treatments. This delay can be considered unacceptable and not ethical in presence of alternatives (both ARNI and SGLT2i) that have shown to reduce morbidity and mortality already after 30 days.
- beyond the beneficial effect on symptoms, both ARNI and SGLT2 'offer' a relevant prolongation of the expected life span. This can justify their early use regardless of the symptomatic response of other drugs already in therapy.
- in addition to the strictly anti heart failure effects, the new drugs exert a wide range of positive actions at metabolic and renal level capable of providing further clinical advantages in the medium-long term.

DS: My God, congratulations Sir. The implementation of your deductive reasoning does apply not only to the scene of crimes, but also to the medical fields. Indeed, as you stated, an ideal detective and an ideal clinician share the same qualities: 'observation, deduction and knowledge'.<sup>13</sup>

SH: Elementary!

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