Biases in how physicians choose to withdraw life support

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Summary

We have investigated biases in physicians' decisions regarding the form of life support to withdraw from critically ill patients in whom the decision to withdraw has already been made. Using a specially designed instrument that solicited both self-reported preferences and also responses to experimentally varied clinical vignettes, we surveyed 862 American internists, of whom 481 (56%) responded. Physicians do have preferences about the form of life support withdrawn. From most likely to least likely the order is: blood products, haemodialysis, intravenous vasopressors, total parenteral nutrition, antibiotics, mechanical ventilation, tube feedings, and intravenous fluids. Four biases in decision making were also identified. Physicians prefer to withdraw forms of therapy supporting organs that failed for natural rather than iatrogenic reasons, to withdraw recently instituted rather than longstanding interventions, to withdraw forms of therapy resulting in immediate death rather than delayed death, and to withdraw forms of therapy resulting in delayed death when confronted with diagnostic uncertainty. Because these biases may have clinical, social, and ethical consequences counter to patient goals, and because they may affect the underlying decision whether to withdraw life support at all, they may represent impediments to rational and compassionate decision making in critical care.

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Introduction

A decision to withdraw life support is best made by patients themselves, and the right of competent adults (or their proxies) to make such decisions is well established. The manner by which critically ill patients should die, however, is usually entrusted to physicians. Since most physicians are uncomfortable with euthanasia, such patients are usually allowed to die by physicians tempering efforts to prolong life and withholding or withdrawing life-sustaining therapy.

In previous studies of end-of-life choices, the decision whether life support should be withdrawn has overshadowed clinical, social, and ethical concerns about how life support is withdrawn. Most research has focused on patients' preferences,[1] on attitudes of health care workers toward withdrawal,[2,3] on the ethics of the decision to withdraw,[4-7] or on factors that influence whether life support is withdrawn (eg, age, quality of life, diagnosis, and disease severity[8,9]). Some studies have looked at the circumstances in which specific forms of life support such as haemodialysis,[10] mechanical ventilation,[11] or food and water,[12,13] might be withdrawn. And there has been some research on how life support is terminated once the decision to withdraw has been made[14-16] and on how physician attitudes influence such decision-making.[17-21] Despite all this, research on the factors that influence physicians' decisions regarding the form of life support to withdraw is limited.

A critically ill patient may be on several types of life support at once, any of which might be withdrawn. Physicians planning to withdraw support must therefore make choices, and their decisions may influence the rapidity, painlessness, and dignity of patients' deaths. Do physicians distinguish between withdrawing different forms of life support? If they do, what influences their decision to stop certain kinds of therapy and not others? We hypothesised that major influences would include the timing of the patient's death with respect to the withdrawal, the degree of diagnostic certainty, the duration of treatment with the form of life support, and the presence of iatrogenic complications. To our knowledge, studies of such influences have not previously been reported.

Survey population and methods

Subjects

We drew our sample from the 862 residents, fellows, and attending physicians affiliated to the department of medicine, University of Pennsylvania, whose addresses were available. These internists, who were on staff at twenty-four community, government, and university hospitals, were sent a 20-page booklet, requiring about 35 min to complete, and a prepaid envelope. They were assured that their participation was voluntary and that responses would be confidential. Those who did not respond within 50 days were sent the booklet again.

Survey instrument

We asked for demographic data, including practice type and intensive care unit (ICU) experience, and invited open-ended comments. The survey instrument also elicited information on how life support might be withdrawn by a fixed set of direct questions about respondents' preferences and by decision-oriented questions accompanying seven clinical vignettes, the versions of which we varied from physician to physician. A fractional factorial design resulted in eight forms of the survey instrument, which were randomly distributed. The instrument was reviewed by two experts in critical care and had been pre-tested on 10 internists.

Direct questions

All participants were asked the same five direct questions, one for each hypothesis (see figure 1 for an example). Participants were allowed to select no preference.

Vignettes

Doctors were asked how they would withdraw life support in response to seven clinical vignettes. In all the vignettes, the patient was terminally ill and comatose, had clearly expressed in advance a desire for life support to be withdrawn under these conditions, and the family agreed with that decision. The decision to withdraw life

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Some physicians may feel differently about withdrawing life-sustaining therapy depending upon whether that therapy supports an organ system that has failed for natural or for iatrogenic reasons. All else being equal, which of the following medical therapies would you *prefer* to withdraw? 1) a treatment that the patient has required because of his underlying disease; or 2) a treatment that the patient has required because of an iatrogenic complication

Figure 1: **Example of direct question**

SL is a 68-year-old patient of yours with no significant past medical history. Eight days ago she suffered a prolonged seizure complicated by hypotension, myoglobinuria, acute renal failure, and severe obtudation. She now requires hemodialysis. A chest x-ray on admission showed a mass in the right mid-lung field. A CT scan of the brain showed multiple brain metastases. You decided a diagnostic bronchoscopy was needed and you consulted a pulmonologist to perform it. Bronchoscopic biopsy of the mass showed squamous cell carcinoma. Her later course was complicated by a massive pulmonary haemorrhage, and she has required mechanical ventilation in addition to hemodialysis.

The patient has required mechanical ventilation and daily dialysis for one week, and her mental status has not improved. SL had previously expressed the wish to her family and to you that should she suffer a medical catastrophe, she would prefer to die rather than be kept alive by artificial means. Because of these previously expressed wishes, her family asks that you withdraw life support.

Figure 2: **Control vignette**

support had already been made. The different versions of each vignette, altered slightly to test our hypotheses, were randomly distributed. For example, four versions of a vignette addressed the hypothesis about iatrogenic complications, and physicians received only one of these. The first version, which served as a control, described a patient in whom both mechanical ventilation and haemodialysis were required because of underlying disease (figure 2). In the second version, the last sentence of the first paragraph was modified. Mechanical ventilation was required because of an iatrogenic complication (figure 3). In the third version, it was the haemodialysis that was required because of an iatrogenic error (a negligent overdose of radiographic contrast) and the mechanical ventilation was required to treat the underlying disease. This version was paired with a second control version in which both haemodialysis and mechanical ventilation were required because of the underlying disease. The two control versions of this vignete were virtually identical.

Unfortunately, through an error in technique, the bronchoscopy was performed with the wrong type of biopsy needle, resulting in a massive pulmonary haemorrhage. Because of this iatrogenic complication, she has required mechanical ventilation in addition to hemodialysis.

Figure 3: **Vignette with iatrogenic complication**

All four versions of the above vignette example were followed by the same three questions, which elicited the likelihood of withdrawing haemodialysis (five-point Likert scale from "very likely" to "very unlikely"), the likelihood of withdrawing mechanical ventilation (using a similar scale), and the preference when asked to choose between withdrawing haemodialysis or ventilation (five-point scale from "much more likely to withdraw haemodialysis" to "much more likely to withdraw mechanical ventilation"). The six other clinical vignettes for the remaining hypotheses, varied in a similar manner, were followed by similarly constructed Likert response scales.

Statistical analysis

The responses to the direct questions were analysed assuming a binomial distribution where there were two response categories and Friedman's test statistic and Wilcoxon's signed-rank test where more than two items were ranked.[22] These tests determine whether, in aggregate, physicians exhibit a systematic preference among the alternative choices. Ties were permitted in ranked items. A paired-sample, Yates corrected chi-squared test, with respondents acting as their own controls, was used to compare responses to similar direct questions within subjects (in the analysis of the influence of expected timing of death under diagnostic uncertainty). Bivariate analyses were conducted with Bonferroni corrected Pearson's chi-squared tests and with logistic regression.

The responses to the questions accompanying the vignettes were analysed by independent sample two-tailed t tests on the differences in mean responses between groups of subjects receiving different versions of the same vignette. Multiple contingency table analysis of ordinal data and the McNemar test of marginal symmetry[23] were used for the within-subjects comparison of response patterns to the questions regarding the influence of timing of death on the selection of form of life support withdrawn.

Consensus rank	Form of life support	Mean rank
1	Blood products	3 27 (most likely to withdraw)
2	Haemodialysis	3 28
3	Intravenous vasopressors	3 75
4	Total parenteral nutrition	3 93
5	Antibiotics	4 73
6	Mechanical ventilation	5 27
7	Tube feedings	5 42
8	Intravenous fluids	6 35 (least likely to withdraw)

For entire rank list, Friedman $\chi^2 = 673\ 6$ (df = 7), suggesting that rankings are non-random ($p < 0\ 0001$). 84 (19%) of the 456 respondents gave all forms of therapy the same rank.

Table 1: **Physician ranking of forms of life support in order of preference for withdrawal**

Results

Sample

Of the study population of 862, 72% were attending physicians and 20% were women. There were 359 responses to the first mailing and another 122 to the second (response rate 56%). Respondents did not differ significantly from non-respondents with respect to attending status, gender, or version of survey instrument received. Because of missing data, not all totals in the analyses equal 481.

The respondents had an average age of 41; 20% were women; 70% were attending physicians, the others being fellows and residents; 55% practised primarily at the University of Pennsylvania Medical Center. The respondents spent an average of 67% of their time in clinical duties (range 0–100%). All subspecialties of internal medicine were represented—eg, 26% were general internists, 18% cardiologists, 9% nephrologists, and 8% pulmonologists.

Experience in the ICU varied. When the physicians were asked how many daily contacts with ICU patients they had in a typical month, 19% reported none, 22% 1–5, 21% 6–19, 22% 20–50, and 16% more than 50. Experience with the withdrawal of life support varied too; in the preceding year, 17% of respondents had not participated in the care of a patient from whom life support was withdrawn, 21% had such experience 1–2 times, 31% 3–5 times, 19% 6–10 times, and 12% more than 10 times.

Type of life support

Our most general hypothesis was that physicians are less likely to withdraw certain medical treatments than others, even though the circumstances and consequences of the withdrawal are in all other respects identical and even though the decision to withdraw had already been made. To test this, physicians were asked to rank their preferences for the withdrawal of eight life-sustaining medical therapies. Systematic preferences emerged (table 1).

Hypothesis	No
Iatrogenic complications:	
"I prefer to withdraw a treatment that . . ."	
"the patient has required because of an iatrogenic complication"	14 (4%)
"the patient has required because of his underlying disease"	303 (96%)
"no preference"	141
Duration of prior treatment:	
"I prefer to withdraw a treatment that . . ."	
"the patient has required for many months"	95 (33%)
"the patient has required for a few days"	190 (67%)
"no preference"	170
Timing of death (certain diagnosis):	
"I prefer to withdraw a treatment that . . ."	
"if withdrawn, will result in death in about a day or two"	70 (19%)
"if withdrawn, will result in death in a few minutes" or "a few hours"	302 (81%)
"no preference"	84
Timing of death (uncertain diagnosis):	
"I prefer to withdraw a treatment that . . ."	
"if withdrawn, will result in death in about a day or two"	134 (40%)
"if withdrawn, will result in death in a few minutes" or "a few hours"	198 (60%)
"no preference"	122

All differences were significant ($p < 0.001$) by the binomial test (iatrogenesis and duration hypotheses) or by the Friedman test (timing hypotheses).

Table 2: **Responses to direct questions**

Each subject also received a clinical vignette describing a terminally ill and comatose patient supported by both intravenous pressor agents and mechanical ventilation, the withdrawal of either of which would result in a gradual and painless death in about four hours. When asked to choose between these two forms of life support, physicians preferred to withdraw vasopressors over mechanical ventilation with a mean response of 2·1 on a five-point Likert scale in which 3·0 indicates no preference ($p < 0.0001$).

Iatrogenic complications

We hypothesised that physicians would be less likely to withdraw a treatment that was supporting an organ system that had failed as a result of iatrogenic complications rather than for natural reasons. Of 317 expressing a preference, 96% were for withdrawal of support required because of an underlying disease (table 2).

We also tested this hypothesis using four versions of one clinical vignette. Compared with the control (both forms of life support required because of underlying disease), physicians were less likely to withdraw mechanical ventilation when it was required because of an iatrogenic complication (mean response 3·4 *vs* 3·8, $p = 0.044$), but there was no difference in the likelihood of withdrawing haemodialysis in this pair of versions. Similarly, in a different pair of versions, physicians were less likely to withdraw haemodialysis when that was required because of an iatrogenic compilation (4·0 *vs* 4·6, $p < 0.001$), but there was no difference in the likelihood of withdrawing mechanical ventilation.

When asked to choose explicitly between haemodialysis and mechanical ventilaton, physicians' responses lent further support to these findings. Preferences were expressed on a Likert scale in which responses close to 1 suggest preference for withdrawal of haemodialysis, whereas responses close to 5 suggest withdrawal of mechanical ventilation. The mean response for the two control versions was 2·3—ie, there was an underlying preference for the withdrawal of haemodialysis. The mean response among those told that the mechanical ventilation was required because of iatrogenic error was 2·1, toward the withdrawal of haemodialysis. Conversely, the mean response among those told that the haemodialysis was required because of an iatrogenic error was 2·5, toward the withdrawal of mechanical ventilation. The difference between the two versions is significant ($p = 0.047$) and suggests that subjects were less likely to withdraw the form of life support required because of an iatrogenic complication regardless of the form of life support involved.

Duration of prior therapy

We hypothesised that physicians would be less likely to withdraw medical treatments when patients had required them for a long time than for a short time. We asked for preferences between an unspecified treatment that the patient had been on for a few days or many months. Of 285 expressing a preference, 67% favoured withdrawal of recently instituted life support (table 2). The vignette for this hypothesis described a patient who required haemodialysis and mechanical ventilation. The three versions of the vignette differed only in that in one both forms of life support were instituted acutely, whereas the other two had ventilation chronic and dialysis acute and dialysis chronic and ventilation acute. The responses indicated a preference for withdrawal of recently instituted support whichever it was, but the differences were not significant.

Timing of death

To test the hypothesis that physicians' decisions are influenced by how soon death is expected after life support is withdrawn participants were asked to rank an unspecified treatment that, if withdrawn, would result in death in a few minutes, a few hours, or a day or two. Of 372 expressing a preference, 81% opted for minutes/hours rather than days (table 2). Two vignettes confirmed this. All subjects received both. In one the physicians were asked to choose between death in 15 min if they withdrew one form of life support versus death in 4 h if they withdrew another; the timings were then reversed and the question was asked again. In the second vignette the clinical setting was different and the timings were 4 h versus 24 h. In both vignettes, the two forms of therapy were intravenous vasopressors and mechanical ventilation. The response suggested that physicians were more likely to withdraw a form of life support resulting in immediate death regardless of the form involved ($p < 0.0001$). Moreover, physicians preferred the more immediate cause of death regardless of the timings being compared; 79% preferred death in 15 min to death in 4 h and 90% preferred death in 4 h to death in 24 h.

Diagnostic uncertainty

We hypothesised that physicians would be less likely to withdraw life support that would result in immediate death when the diagnosis was unknown, even if knowing it would modify neither prognosis nor therapy and even if the decision to withdraw had already been made. For a patient with a poor prognosis but for whom the cause of organ failure was not known, physicians were asked to rank the withdrawal of an unspecified treatment, and there was a shift in individual respondents' preferences towards death in days (40% compared with only 19% when the diagnosis was certain, $p < 0.0001$, table 2).

Physicians' social and professional characteristics

We found no significant association of any of the above decision biases with the physicians' sex, religion, rank, specialty, percent of time spent in clinical practice, number

of patients from whom life support had been withdrawn in the previous year, or number of patients visited in the ICU in the previous month.

Discussion

Our research shows that physicians' preferences about the type of life support to withdraw are influenced by iatrogenic complications, duration of therapy with each form of life support, expected timing of death, and diagnostic uncertainty. These decision biases were elicited in situations wherein the decision to withdraw life support and to cease efforts to save the patient's life had already been made and wherein the patients were comatose and terminally ill and had expressed clear wishes about life support. Not all patients in whom life support is withdrawn meet these criteria, but such patients are among those in whom the withdrawal of life support should be the least controversial and the least subject to the biases we identified.

A physician who prefers not to withdraw forms of life support required because of iatrogenic complications may be wishing to avoid all involvement with error[24] or may fear possible legal entanglement. Those who choose not to withdraw long-term life support may associate such support with the status quo and perceive its withdrawal as more unusual or aggressive.[25] Physicians who pefer death to be delayed, a minority in this study, may feel that some blame may attach to them if their actions and the death come close together. Physicians who prefer to temporise in the face of diagnostic uncertainty may desire to avoid irrevocable decisions.[26] In our view, however, once the decision to withdraw life support has been made, humanity should be the primary concern in decisions about how that is done,[27] and many of the factors that seem to influence physicians' decisions ought to be irrelevant. For example, why choose to withdraw a form of life support that results in delayed death when the decision to withdraw life support itself has already been made, especially where the diagnosis is unknown but is irrelevant? And not withdrawing a therapy required because of an iatrogenic error, as opposed to one required to treat an underlying disease, adds a faulty decision to a mistake. The decision biases that we have identified here may, in some circumstances, prolong the period of dying, increase the suffering of patients and their families, and waste resources. These findings also raise concerns about patient autonomy. Patients, when formulating advance directives, tend not to make distinctions among various forms of life support.[28,29] Some physicians, it seems, do. Should, therefore, advance directives be drafted to specify how life support could be withdrawn? We think not: rather than seek such specificity physicians should focus on the underlying goals.[30,31]

Our study has limitations. First, we studied preferences expressed in response to direct questions and hypothetical scenarios rather than behaviour in real clinical settings. Our vignettes did not permit interaction with colleagues or with patients' families. Nevertheless, many respondents did indicate that they thought their responses to the hypothetical cases accurately reflected their behaviour. Second, we restricted responses to the withdrawal of a single form of life support; in reality more than one form of support may be withdrawn at the same time. However, our respondents (and others[15]) suggest that forms of life support are often withdrawn in sequence. Third, despite being told that death would be identical regardless of the form of therapy withdrawn, respondents may not always have accepted it—although randomisation of the vignettes should control for this.

Our results suggest that some physicians are biased when they choose how to withdraw life support. Because these influences may not be relevant to patient goals, clinicians should re-evaluate their practices in this regard. Indeed, an understanding of physicians' preferences on how to withdraw life support provides a window back on whether they decide to withdraw life support. If a patient is on only one form of support, a physician's unwillingness to withdraw therapy due to one of the biases we have identified could result in the continuation of support despite the patient's and the family's wishes. Withdrawing life support in critically ill patients may depend not just on ethical principles and clinical details but also on physicians' concerns about the manner in which support will be withdrawn.

The primary goal in life support withdrawal ordinarily is to allow the patient to die as humanely as possible, and the decision should be made in the most ethically sensitive, logically rigorous, and clinically appropriate way possible. The biases we have identified may subvert this objective.

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References

1 Danis M, Patrick DL, Southerland LI, Green ML. Patients' and families' preferences for medical intensive care. *JAMA* 1988; **260:** 797–802.

2 Solomon MZ, O'Donnell L, Jennings B, et al. Decisions near the end of life: professional views on life-sustaining treatments. *Am J Public Health* 1993; **83:** 14–23.

3 Zussman R. Intensive care: medical ethics and the medical profession. Chicago: University of Chicago Press, 1992.

4 Emanuel EJ. Should physicians withhold life-sustaining care from patients who are not terminally ill? *Lancet* 1988; i: 106–08.

5 Ruark JE, Raffin TA, and The Stanford University Medical Center Committee on Ethics. Initiating and withdrawing life support: principles and practice in adult medicine. *N Engl J Med* 1988; **318:** 25–30.

6 Weir RF. Abating treatment with critically ill patients. New York: Oxford University Press, 1989.

7 President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Deciding to forego life-sustaining treatment—ethical, medical, and legal issues in treatment decisions. Washington, DC: US Government Printing Office, 1983.

8 Crane D. The sanctity of social life: physicians' treatment of critically ill patients. New Brunswick, NJ: Transaction Press, 1977.

9 Uhlmann RF, Pearlman RA. Perceived quality of life and preferences for life-sustaining treatment in older adults. *Arch Intern Med* 1991; **151:** 495–97.

10 Neu S, Kjellstrand CM. Stopping long-term dialysis: an empirical study of withdrawal of life-supporting treatment. *N Engl J Med* 1986; **314:** 14–20.

11 Schneiderman LJ, Spragg RG. Ethical decisions in discontinuing mechanical ventilation. *N Engl J Med* 1988; **318:** 984–88.

12 Institute of Medical Ethics Working Party on the Ethics of Prolonging Life and Assisting Death. Withdrawal of life support from patients in a persistent vegetative state. *Lancet* 1991; **337:** 96–98.

13 Lynn J, ed. By no extraordinary means: the choice to forgo life-sustaining food and water. Bloomington: Indiana University Press, 1989.

14 Wilson WC, Smedira NG, Fink C, McDowell JA, Luce JM. Ordering and administration of sedatives and analgesics during the withholding and withdrawal of life support from critically ill patients. *JAMA* 1992; **267:** 949–53.
15 Smedira NG, Evans BH, Grais LS, et al. Withholding and withdrawal of life support from the critically ill. *N Engl J Med* 1990; **322:** 309–15.
16 Faber-Langendoen K, Bartels DM. Process of foregoing life sustaining treatment in a university hospital: an empirical study. *Crit Care Med* 1992; **20:** 570–77.
17 Pearlman R, Inui TS, Carter WB. Variability in physician bioethical decision-making. *Ann Intern Med* 1982; **97:** 420–25.
18 Caralis PV, Hamond JS. Attitudes of medical students, housestaff, and faculty physicians towards euthanasia and termination of life-sustaining treatment. *Crit Care Med* 1992; **20:** 683–90.
19 Nightingale SD, Grant M. Risk preference and decision making in critical care situations. *Chest* 1988; **93:** 684–87.
20 Von-Preyss-Friedman SM, Uhlmann RF, Cain KC. Physicians' attitudes toward tube feeding chronically ill nursing home patients. *J Gen Intern Med* 1992; **7:** 46–51.
21 Charlson ME, Sax FL, MacKenzie R, Fields AD, Braham RL, Douglas G. Resuscitation: how do we decide? A prospective study of physicians' preferences and the clinical course of hospitalized patients. *JAMA* 1986; **255:** 1316–22.
22 Hollander M, Wolfe DA. Nonparametric statistical methods. New York: John Wiley & Sons, 1973.
23 Everitt BS. The analysis of contingency tables. London: Chapman and Hall, 1977.
24 Cohen BJ, Pauker SG. How do physicians weigh iatrogenic complications? *Medical Decision Making* 1992; **12:** 350 (abstr).
25 Samuelson W, Zeckhauser R. Status quo bias in decision making. *J Risk Uncertainty* 1988; **1:** 7–59.
26 Bosk CL. Occupational rituals in patient management. *N Engl J Med* 1980; **303:** 71–76.
27 Cassell EJ. The nature of suffering and the goals of medicine. New York: Oxford Univeristy Press, 1991.
28 Emanuel LL, Barry MJ, Stoeckle JD, Ettelson LM, Emanuel EJ. Advance directives for medical care—a case for greater use. *N Engl J Med* 1991; **324:** 889–95.
29 Danis M, Southerland LI, Garrett JM, et al. A prospective study of advance directives for life-sustaining care. *N Engl J Med* 1991; **324:** 882–88.
30 Brett AS. Limitation of listing specific medical interventions in advance directives. *JAMA* 1991; **266:** 825–28.
31 Mower WR, Baraff LJ. Advance directives: effect of type of directive on physicians' therapeutic decisions. *Arch Intern Med* 1993; **153:** 375–81.

HLA-B27-restricted CD8 T cells derived from synovial fluids of patients with reactive arthritis and ankylosing spondylitis

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Summary

Ankylosing spondylitis and seronegative spondylarthropathies such as Reiter's syndrome and reactive arthritis are strongly associated with HLA-B27. However, the mechanisms by which HLA-B27 is involved in disease susceptibility and pathogenesis are unknown. If the disease association is a consequence of HLA-B27's physiological function in antigen presentation, the disease should be mediated by cytotoxic T lymphocytes (CTLs) that recognise bacterial or self peptides presented by HLA-B27. Proof of this arthritogenic peptide model requires isolation of B27-restricted CD8 T cells from arthritic joints of patients with spondylarthropathies. An important question is whether "arthritogenic" bacteria such as yersinia or salmonella can generate HLA-B27-restricted bacteria-specific CTLs. We describe such HLA-B27-restricted CTLs.

We tested a panel of 354 αβ-TCR CD8 T lymphocyte clones (TLCs) that had been derived from the synovial fluid of 4 patients with reactive arthritis and 2 patients with ankylosing spondylitis. In 1 patient with yersinia-induced arthritis, 2 TLCs were identified that killed specifically yersinia-infected B27 target cells. In another patient with salmonella-induced arthritis, 1 B27-restricted CD8 TLC that recognised both salmonella and yersinia was identified. In 5 of the 6 patients autoreactive CTLs were found, 5 of which showed B27-restricted killing of uninfected cell lines.

B27-restricted CTLs with specificity for arthritogenic bacteria or autoantigens provide a missing link in the pathogenesis of the HLA-B27-associated spondylarthropathies.

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Introduction

Some infections of the gastrointestinal or genitourinary tract, such as yersiniosis, salmonellosis, campylobacter enteritis, shigellosis, or chlamydial urethritis, precipitate characteristic arthritic syndromes including reactive arthritis and Reiter's syndrome in genetically susceptible individuals.[1-4] The high prevalence of the HLA B27 antigen in patients with these syndromes and the syndromes' clinical similarities have linked reactive arthritis and Reiter's syndrome to the so called HLA-B27-associated seronegative spondylarthropathies such as ankylosing spondylitis.

Local T-cellular immune responses to the triggering microorganisms seem to have a crucial role in the pathogenesis, maintenance, and resolution of reactive arthritis. T-lymphocyte clones (TLCs) with specificity for arthritogenic bacteria have been grown and characterised from the synovial fluids of patients with yersinia,[5,6] salmonella,[7] and chlamydia-induced[8] reactive arthritis. All these clones exhibited the CD4 phenotype and were restricted by HLA-DR[5,6] or HLA-DP.[8] The problem is that CD4 T cells cannot account for the role of HLA-B27, which is a restriction element for CD8 cells. The TLCs specific for yersinia antigens belong predominantly to the T_h1 subset of helper T cells and it seems likely that they are generated in the host as part of the defence mechanism that