

Immunologic Cross-Reactivity between Penicillins and Cephalosporins: A Review

Lawrence D. Petz

From the Institutes of Medical Sciences and the University of California, San Francisco, California

Several approaches have been undertaken in the study of possible immunologic cross-reactivity between cephalosporins and penicillins. Although the chemical structures of these compounds are similar in several respects, there are distinct differences in their degradation and transformation. Various degrees of cross-reactivity of antibodies produced in response to administration of these drugs have been demonstrated both with test systems that measure IgG and IgM antibodies and with those that measure IgE antibodies. The clinical significance of immune responses to cephalosporins is best understood in regard to immunohematologic abnormalities: positive direct antiglobulin (Coombs') tests occur in only ~3% of patients receiving cephalosporins; however, several cases of cephalosporin-induced immune hemolytic anemia have been reported. Clinical studies of the cephalosporins indicated that patients with a history of penicillin allergy have an increased incidence of reactivity to cephalosporins, but it is impossible to determine to what extent this finding is due to immunologic cross-reactivity because penicillin-allergic patients have an increased incidence of hypersensitivity reactions to drugs immunologically unrelated to penicillins. In addition, there is evidence of specific immune response to cephalosporins that indicates independently acquired hypersensitivity rather than cross-reactivity in some patients.

The possibility of immunologic cross-reactivity between cephalosporins and penicillins is of frequent concern in clinical medicine. A variety of approaches have been undertaken in the study of possible cross-reactivity and the assessment of its clinical significance.

In this review, the following aspects will be considered: (1) chemical configuration and degradation of penicillins and cephalosporins, (2) antibody cross-reactivity, (3) immunohematologic reactions, (4) immediate hypersensitivity reactions, and (5) clinical studies.

Chemical Configuration and Degradation of Penicillins and Cephalosporins

Perhaps the first scientists to consider immune cross-reactivity were chemists who noted that the chemical configurations of the basic structures of the penicillins and cephalosporins (6-amino-

penicillanic acid [6-APA] and 7-amino-cephalosporanic acid [7-ACA], respectively) are similar in several respects. Both compounds are of low molecular weight, are highly substituted, possess a β -lactam ring structure on which antimicrobial activity depends, and possess a separate ring structure containing sulfur [1]. However, the chemistry of the degradation and transformation of the penicillins differs from that of the cephalosporins [2]. After the action of specific β -lactamases, penicillin forms a stable penicilloate, whereas cephalosporin forms an ultraviolet absorption peak that rapidly disappears, a phenomenon indicating fragmentation of the cephalosporin nucleus.

Thus, on the basis of the chemical configuration and degradation of the penicillins and cephalosporins, some authors have suggested that immunologic cross-reactivity between these compounds would be expected [3, 4], whereas others have come to the opposite conclusion [2, 5, 6]. However, even more detailed information on the chemistry and degradation of penicillins and cephalosporins than is presently available will not produce a definitive answer regarding the presence or absence of *in vivo* immunologic cross-reactivity.

This work was supported in part by a grant from Eli Lilly and Company.

Please address requests for reprints to Dr. Lawrence D. Petz, Hematology-Immunology Research Unit, 2200 Webster Street, Room 229, San Francisco, California 94115.

Cross-Reactivity of Antibodies to Penicillins and Cephalosporins

Another approach has been the assessment of cross-reactivity of antibodies to penicillins and cephalosporins in animals and in humans. Schneierson et al. [7] reported in 1964 that cephalothin can stimulate the production of immunologic reactions in rabbits and guinea pigs, but they found no evidence of cross-reactions between cephalothin and penicillin. Working with rabbits, Brandriss et al. [8] and Batchelor et al. [9] demonstrated that cephalothin and cephaloridine conjugated to appropriate protein carrier molecules can induce the formation of antibodies detectable by HA, precipitation, and passive cutaneous anaphylaxis, and that these antibodies cross-react with the major antigenic determinant of penicillin, i.e., the benzyl-penicilloyl determinant. Abraham et al. [10] were the first investigators to report results with use of human sera. They studied 174 adult patients receiving cephalothin or penicillin G iv. Utilizing passive HA, these workers demonstrated the immunogenicity of cephalothin as indicated by a higher incidence of antibodies to cephalothin in patients who had received the drug than in controls and by an increase in titer of antibodies to cephalothin during administration of the drug. Immunologic cross-reactivity with penicillin was indicated by a high incidence of antibodies to cephalothin in patients who were receiving penicillin and had never received cephalothin, and by an increase in titer of antibody to cephalothin in patients receiving penicillin. Furthermore, patients receiving cephalothin had a high incidence of antibodies to penicillin, and the titer of antibody to penicillin increased during administration of cephalothin. Inhibition of HA by derivatives of penicillin and cephalothin and absorption of sera with erythrocytes sensitized with penicillin or cephalothin confirmed the cross-reactivity. Such HA antibodies are primarily, if not exclusively, of the IgM and IgG classes.

Petersen and Graham [11] studied the immunologic cross-reactivity of cephalexin and penicillin. Utilizing passive HA and serum antibodies from rabbits, they reported that antibody to cephalexin appears to be directed primarily to the 7-ACA nucleus and does not cross-react with

the penicillin nucleus. Indeed, the concentration of penicillin G required to inhibit antibody to cephalexin was 600 times the concentration of cephalexin needed for inhibition. Similarly, the amount of cephalexin necessary to inhibit antibody to penicillin G was approximately 30 times the concentration of penicillin G needed for inhibition. Also, experiments with human sera in which IgE antibodies were measured with use of a rat mast cell degranulation technique generally supported the conclusion that the molecules of cephalexin and penicillin G are sufficiently dissimilar immunologically that antibodies stimulated by the presence of one of the antibiotics do not readily recognize antibodies to the other.

Assem and Vickers [12] studied the immunologic cross-reactivity between penicillins and cephaloridine in 24 patients with established allergy to penicillin. These investigators used a variety of immunologic tests which included HA, skin tests, quantitative leukocyte challenge in which histamine release by allergen was estimated, and lymphocyte stimulation. Cross-reactivity was clearly established in the majority of patients. The highest percentage of cross-reactivity was demonstrated in the leukocyte challenge test (80%) followed by the lymphocyte stimulation test (50%) and the skin test (46%). None of 10 nonallergic controls gave a positive result in these tests.

Thus, several groups of investigators have rather convincingly demonstrated various degrees of cross-reactivity of antibodies to penicillins and cephalosporins. However, it is not possible to make definitive clinical recommendations, particularly in regard to individual patients, on the basis of such experimental data. Additional approaches are necessary to determine the clinical significance of such information in regard to specific clinical manifestations of immunologic reactivity.

Immunohematologic Reactions

The knowledge that iv administration of large doses of penicillin can result in positive direct antiglobulin (Coombs') tests and immunohemolytic anemia [13] led to concern that similar findings may result from administration of cephalosporins. Studies to investigate this possibility

have led to a rather detailed assessment of the mechanism, laboratory means of evaluation, and clinical significance of penicillin- and cephalosporin-induced immunohematologic reactions.

Early reports regarding several small series of patients indicated that a high percentage of patients receiving cephalosporins developed a positive antiglobulin test [14, 15]. However, a prospective study in which more than 600 direct antiglobulin tests were performed on multiple samples from 169 patients receiving penicillin(s) iv (mainly penicillin G) and 124 patients receiving cephalosporin drugs (primarily cephalothin) indicated that five patients receiving penicillin and four receiving cephalosporins had positive direct antiglobulin tests, i.e., an incidence of ~3% in each instance [10, 16, 17]. A review by Swisher supported the lower figures of incidence [18]. In studies concerning the mechanism and clinical significance of the direct antiglobulin tests that were positive as a result of cephalosporin administration, three mechanisms were proposed.

(1) The cell membrane may be modified by the drug so that the cell takes up proteins non-immunologically [14-16]. In vitro studies indicated that cephalosporin-sensitized cells incubated in normal plasma become coated with albumin, IgG, IgA, IgM, α_1 -antitrypsin, α_2 -macroglobulin, C3, C4, and fibrinogen [16, 19].

(2) The drug may combine with the red blood cell membrane, as does penicillin, and react with cross-reacting antibodies to penicillin [10, 14, 16, 20, 21].

(3) The drug may combine with the red blood cell membrane in a fashion similar to that of penicillin, and specific antibodies to the cephalosporin may react with the drug on the cell [16, 22, 23].

Spath et al. [16] confirmed that all three of these mechanisms may lead to a positive direct antiglobulin test. Whether the positive direct antiglobulin test results from nonimmunologic protein absorption or from fixation of antibody may be determined by serologic tests [19, 24] and is of clinical significance since hemolytic anemia has not been reported as a result of nonimmunologic protein absorption.

Although the direct antiglobulin test has been most extensively studied with cephalothin, positive tests have also been ascribed to other cepha-

losporins, such as cephalexin [25-27], cephaloridine [28, 29], and cefazolin [26, 30].

The principal clinical importance of positive direct antiglobulin tests caused by cephalosporins is that they cause apparent incompatibility in the minor cross-match test and may confuse the evaluation of hemolytic disorders of other etiology [17, 31, 32]. Since penicillin is the second most common cause of drug-induced immune hemolytic anemia, and since the mechanism of red blood cell sensitization with cephalosporins is, in some cases, similar to that resulting from administration of penicillin, Abraham et al. [10] stated in 1968 that it was "surprising" that hemolytic anemia due to administration of cephalosporins had not been reported. Since that time several cases of cephalosporin-induced immunohemolytic anemia have been reported [22, 33-35], but such cases are much rarer than those occurring during penicillin therapy. This finding may be due to the fact that neither the drug nor the complex of drug with antibody to the drug is firmly bound to erythrocytes during therapeutic administration of cephalosporins [10].

Neutropenic reactions [36, 37] and thrombocytopenia [38, 39] have also been described and may be caused by an immune mechanism but are less well characterized.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions must be considered separately from immunohematologic reactions since IgG and IgM HA antibodies, which are of significance in regard to hematologic reactions, do not mediate immediate hypersensitivity reactions. Such reactions are apparently mediated by IgE antibodies, which may be demonstrated by immunologic methods such as skin tests, histamine release by leukocytes, and radioimmunoassay.

Skin tests have been studied rather extensively in penicillin allergy [40-44], and although these tests are helpful, most investigators agree that there is not a 100% correlation of results from skin tests with the presence or absence of immediate hypersensitivity reactions [40]. Nevertheless, these tests are helpful in assessing the probability of an accelerated reaction to penicillin. For example, Levine and Zolov [42] reported that an

accelerated reaction occurred in only one of 185 skin test-negative patients as compared with eight of 11 skin test-positive patients treated with penicillin. Similarly, Green and Rosenblum reported that only one of 92 skin test-negative patients reacted to penicillin, whereas two of eight skin test-positive patients reacted [44]. Levine stated that "negative skin tests for benzylpenicilloyl-specific and minor-determinant-specific skin-sensitizing antibodies appear to rule out the possibility of an immediate or accelerated allergic reaction" [41], and he attributed the less definitive experiences with skin tests by others to the fact that the skin test reagents used by others have not included the "minor determinant mixture" [45]. Apparently, Levine's work with the "minor determinant mixture" has not been confirmed by other investigators, at least in part because the chemical nature of the "minor determinants" has not been elucidated [46]. This lack of knowledge hinders further work on the nature and significance of immune responses of minor determinant specificities [46].

Only a limited number of studies have been done using skin tests with cephalosporin drugs [4, 12, 47-49], and these studies have demonstrated that a minority of patients allergic to penicillin have positive skin tests to cephalosporins. However, the clinical significance of such reactions has not been determined. Thus, much more extensive data are needed before results from skin tests could be shown to be of value in regard to hypersensitivity to cephalosporins and possible cross-reactivity with penicillins.

Other methods of assaying IgE antibodies include rat mast cell degranulation [11], release of histamine from sensitized human leukocytes [12], and radioimmunoassay. The last technique has been applied to penicillin allergy with promising results [50-52] and may prove to be a reliable *in vitro* assay for the presence of IgE antibodies to a drug. A particular advantage of radioimmunoassay is that it is commonly utilized in clinical laboratories, whereas other methods, such as release of histamine from human leukocytes, are not. Therefore, radioimmunoassay could be widely applied if further experience indicates its reliability. To date, however, there are no published data regarding the use of radioimmunoassay of IgE antibodies to cephalosporins.

Clinical Studies

Although the weight of presently available laboratory data supports the concept of immunologic cross-reactivity between various penicillins and cephalosporins, one cannot utilize such experimental data to predict accurately the effect of administration of cephalosporins to individual patients with a history of allergy to penicillin. Lacking specific predictive immunologic tests, one must refer to clinical studies to obtain additional information regarding immunologic cross-reactivity. During clinical trials conducted with the cephalosporins, 15,708 case reports were evaluated (R. S. Griffith and H. R. Black, personal communication). Table 1 shows the number of allergic reactions reported after administration of each of several cephalosporins to penicillin-allergic and nonallergic patients. Of the 15,708 patients, 701 (4.5%) had a history of allergy to penicillin, and 57 (8.1%) of these had an allergic reaction to administration of cephalosporins. There were 15,007 patients who did not have a history of penicillin allergy, and 285 (1.9%) of these had an allergic reaction to cephalosporins. Thus, it appears that a patient is about four times more likely to have an allergic reaction to a cephalosporin if he has a history of allergy to penicillin than if he has a negative history of allergy to penicillin.

With use of presently available data, it is im-

Table 1. Allergic reactions to cephalosporins in penicillin-allergic and nonallergic patients.

Cephalosporin, history of penicillin allergy (no. of patients)	No. with allergic reactions (%)
Cephaloridine	
No (3,471)	86 (2.6)
Yes (109)	14 (13.0)
Cephalothin	
No (1,045)	21 (2.0)
Yes (138)	8 (5.8)
Cephalexin	
No (7,819)	87 (1.1)
Yes (291)	19 (6.5)
Cefazolin	
No (1,369)	8 (0.6)
Yes (74)	3 (4.0)
Cefamandole	
No (1,303)	83 (6.4)
Yes (89)	13 (14.6)

possible to ascertain to what extent this higher rate of reactivity to cephalosporins in penicillin-allergic patients can be attributed to immunologic cross-reactivity between penicillin and cephalosporins. Smith et al. [40] showed that in penicillin-allergic individuals there is an increased incidence of hypersensitivity reactions to drugs immunologically unrelated to penicillin. That is, their data indicate that the history of a prior reaction to immunologically unrelated drugs was about three times as frequent in patients without penicillin reactions. In addition, there is evidence of specific immune response to cephalosporins with antibodies that do not cross-react with penicillins [10, 16, 23], a finding indicating independently acquired hypersensitivity rather than cross-allergenicity in some patients [23].

Conclusions

In deciding whether to utilize a cephalosporin in a patient with a history of allergy to penicillin, physicians must first consider that a specific immunologic test to predict such hypersensitivity in an individual patient is not presently available. Physicians should also be aware of the data cited above regarding possible immune cross-reactivity and the clinical studies indicating the limitations concerning the interpretation of these studies. Of equal importance, physicians must consider the comparative efficacy of possible alternative drugs and be aware of the adverse reactions that may result from the use of such alternative antibiotics. Clinical judgment, based on the above approach, allows for the best possible assessment of the advisability of the use of a cephalosporin that can be made in an individual patient, utilizing currently available information.

In general terms, it is perhaps best to avoid the use of cephalosporins, except for compelling reasons, in patients with a past history of anaphylaxis or other immediate-type penicillin hypersensitivity reactions [53]. On the other hand, the above analysis of comparative efficacy and risks makes it reasonable to use cephalosporins for appropriate infections in most patients with a history of a less severe type of allergic reaction to the penicillins. Continued research to develop practical in vitro tests to predict hyper-

sensitivity reactions in individual patients is urgently needed.

References

1. Hewitt, W. L. The cephalosporins—1973. *J. Infect. Dis.* 128 (Suppl.):S312-S313, 1973.
2. Newton, G. G. F., Hamilton-Miller, J. M. T. Cephaloridine: chemical and biochemical aspects. *Postgrad. Med. J.* 43:10-13, 1967.
3. Scholand, J. F., Teenenbaum, J. I., Cerilli, J. G. Anaphylaxis to cephalothin in a patient allergic to penicillin. *J.A.M.A.* 206:130-132, 1968.
4. Grieco, M. H. Cross-allergenicity of the penicillins and the cephalosporins. *Arch. Intern. Med.* 119:141-145, 1967.
5. Abraham, E. P. *The chemistry of new antibiotics*. *Am. J. Med.* 39:692-696, 1965.
6. Flynn, E. H. Biological and chemical studies of the cephalosporins. *Antimicrob. Agents Chemother.* 1966:715-727, 1967.
7. Schneerson, S. S., Perlman, E., Shore, R. Cephalothin antigenicity and cross reactivity with penicillin G. *Clin. Med.* 71:933-937, 1964.
8. Brandriss, M. W., Smith, J. W., Steinman, H. G. Common antigenic determinants of penicillin G, cephalothin and 6-amino-penicillanic acid in rabbits. *J. Immunol.* 94:696-704, 1965.
9. Batchelor, F. R., Dewey, J. M., Weston, R. D., Wheeler, A. W. The immunogenicity of cephalosporin derivatives and their cross-reaction with penicillin. *Immunology* 10:21-34, 1966.
10. Abraham, G. N., Petz, L. D., Fudenberg, H. H. Immunohaematological cross-allergenicity between penicillin and cephalothin in humans. *Clin. Exp. Immunol.* 3:343-357, 1968.
11. Petersen, B. H., Graham, J. Immunologic cross-reactivity of cephalixin and penicillin. *J. Lab. Clin. Med.* 83:860-870, 1974.
12. Assem, E. S. K., Vickers, M. R. Tests for penicillin allergy in man. *Immunology* 27:255-269, 1974.
13. Petz, L. D., Fudenberg, H. H. Coombs-positive hemolytic anemia caused by penicillin administration. *N. Engl. J. Med.* 274:171-178, 1966.
14. Gralnick, H. R., Wright, L. D., McGinniss, H. M. Coombs' positive reactions associated with sodium cephalothin therapy. *J.A.M.A.* 199:725-726, 1967.
15. Molthan, L., Reidenberg, M. M., Eichman, M. F. Positive direct Coombs' tests due to cephalothin. *N. Engl. J. Med.* 277:123-125, 1967.
16. Spath, P., Garratty, G., Petz, L. D. Studies on the immune response to penicillin and cephalothin in humans. *J. Immunol.* 107:860-869, 1971.
17. Petz, L. D. Immunologic reactions of humans to cephalosporins. *Postgrad. Med. J.* 47(Suppl.):64-69, 1971.
18. Swisher, S. N. Antibiotics and red blood cells. In N. V. Dimitrov and J. H. Nodine [ed.]. *Drugs and hemato-*

- logic reactions. Grune and Stratton, New York, 1974.
19. Garratty, G., Petz, L. D. Drug-induced immune hemolytic anemia. *Am. J. Med.* 58:398-407, 1975.
 20. Gralnick, H. R., McGinniss, M. H. Immune cross-reactivity of penicillin and cephalothin. *Nature (Lond.)* 216:1026-1027, 1967.
 21. Nesmith, L. W., Davis, J. W. Hemolytic anemia caused by penicillin. *J.A.M.A.* 203:27-30, 1968.
 22. Gralnick, H. R., McGinniss, M. H., Elton, W., McCurdy, P. Hemolytic anemia associated with cephalothin. *J.A.M.A.* 217:1193-1197, 1971.
 23. Abraham, G. N., Petz, L. D., Fudenberg, H. H. Cephalothin hypersensitivity associated with anti-cephalothin antibodies. *Int. Arch. Allergy Appl. Immunol.* 34:65-74, 1968.
 24. Petz, L. D. Autoimmune and drug-immune hemolytic anemias. In N. R. Rose and H. Friedman [ed.]. *Manual of clinical immunology*. American Society of Microbiology, Washington, D.C., 1976, p. 527-541.
 25. Kosakai, N., Miyakawa, C. Fundamental studies on the positive Coombs' tests due to cephalosporins. *Postgrad. Med. J.* 46:107-109, 1970.
 26. Kuwahara, S., Mine, Y., Nishida, M. Immunogenicity of Cefazolin®. *Antimicrob. Agents Chemother.* 10:374-379, 1970.
 27. Schwarz, S., Gabl, R., Huber, H., Spath, P. Positive direct antiglobulin (Coombs') test caused by cephalixin administration in humans. *Vox Sang.* 29:59-65, 1975.
 28. Fass, R., Perkins, R., Saslow, S. Positive direct Coombs' tests associated with cephaloridine therapy. *J.A.M.A.* 213:121-123, 1970.
 29. York, P., Landes, R., Seay, L. Coombs' positive reactions associated with cephaloridine therapy. *J.A.M.A.* 206:1086, 1968.
 30. Mine, Y., Nishida, M. Studies on direct Coombs reaction by cefazolin in vitro. *J. Antibiot.* 23:575-580, 1970.
 31. Petz, L. D., Fudenberg, H. H. Immunologic mechanisms in drug-induced cytopenias. *Prog. Hematol.* 9:185-206, 1975.
 32. Petz, L. D., Garratty, G. Drug-induced haemolytic anaemia. *Clin. Haematol.* 4:181-197, 1975.
 33. Jeannet, M., Block, A., Dayer, J. M., Farquet, J. J., Girard, J. P., Cruchaud, A. Cephalothin-induced immune hemolytic anemia. *Acta Haematol.* 55:109-117, 1976.
 34. Kaplan, K., Reisberg, B., Weinstein, L. Cephaloridine—studies of therapeutic activity and untoward effects. *Arch. Intern. Med.* 121:17-23, 1968.
 35. Forbes, C. D., Craig, J. A., Mitchell, R., McNicol, G. P. Acute intravascular hemolysis associated with cephalixin therapy. *Postgrad. Med. J.* 48:186-188, 1972.
 36. Davis, A., Seligman, S. J., Hewitt, W. L., Finegold, S. M. Neutropenic reaction to cephalothin therapy. *Antimicrob. Agents Chemother.* 3:272-277, 1963.
 37. Silber, S. J., Diokno, A. Agranulocytosis from cephalosporins. *J.A.M.A.* 224:1427, 1973.
 38. Sheiman, L., Spielvogel, A. E., Horowitz, H. I. Thrombocytopenia caused by cephalothin sodium. *J.A.M.A.* 203:601-603, 1968.
 39. Gralnick, H. R., McGinniss, M., Halterman, R. Thrombocytopenia with sodium cephalothin therapy. *Ann. Intern. Med.* 77:401-404, 1972.
 40. Smith, J. W., Johnson, J. E., Cluff, L. E. Studies on the epidemiology of adverse drug reactions. *N. Engl. J. Med.* 274:998-1002, 1966.
 41. Levine, B. B. Immunologic mechanisms of penicillin allergy. *N. Engl. J. Med.* 275:1115-1125, 1966.
 42. Levine, B. B., Zolov, D. M. Prediction of penicillin allergy by immunological tests. *J. Allergy* 43:231-244, 1969.
 43. Adkinson, N. F., Thompson, W. L., Maddrey, W. C., Lichtenstein, L. M. Routine use of penicillin skin testing on an inpatient service. *N. Engl. J. Med.* 285:22-24, 1971.
 44. Green, G. R., Rosenblum, A. Report of the penicillin study group—American Academy of Allergy. *J. Allergy Clin. Immunol.* 48:331-343, 1971.
 45. Levine, B. B. Allergy to penicillin. *N. Engl. J. Med.* 276:352, 1967.
 46. Levine, B. B. Antigenicity and cross-reactivity of penicillins and cephalosporins. *J. Infect. Dis.* 128 (Suppl.): S364-S366, 1973.
 47. Girard, J. P. Common antigenic determinants of penicillin G, ampicillin and the cephalosporins demonstrated in man. *Int. Arch. Allergy Appl. Immunol.* 33:428-438, 1968.
 48. Steward, G. T. Cross-allergenicity of penicillin G and related substances. *Lancet* 1:509-510, 1962.
 49. Perkins, R. L., Saslaw, S. Experience with cephalothin. *Ann. Intern. Med.* 74:13-24, 1966.
 50. Wide, L., Juhlin, L. Detection of penicillin allergy of the immediate type of radioimmunoassay of reagents (IgE) to penicilloyl conjugates. *Clin. Allergy* 1:171-177, 1971.
 51. Juhlin, L., Wide, L. IgE antibodies and penicillin allergy. In C. H. Dash and H. E. H. Jones [ed.]. *Mechanisms in drug allergy*. Churchill, Livingstone, Edinburgh and London, 1972, p. 139-147.
 52. Kraft, D., Wide, L. Clinical patterns and results of radioallergosorbent test (RAST) and skin tests in penicillin allergy. *Br. J. Dermatol.* 94:593-601, 1976.
 53. Moellering, R. C., Swartz, M. N. The new cephalosporins. *N. Engl. J. Med.* 294:24-28, 1976.