Should Gangrenous Appendicitis Be Labeled as Complicated? An 8-year Single-Center Retrospective Review

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ABSTRACT **Background:** Gangrenous appendicitis falls to the midpoint of the continuum between uncomplicated and complicated appendicitis. We present an eight-year single-center retrospective review of uncomplicated, complicated and gangrenous appendicitis.

Objectives: To analyze the presentation of gangrenous appendicitis in our population.

Methods: We reviewed the presentation, as well as the laboratory, surgical, and pathological findings for complicated, uncomplicated, and gangrenous appendicitis. Logistic regression analysis was conducted to identify predictors of gangrenous and of complicated appendicitis.

Results: During the study period, 865 children had uncomplicated appendicitis and 134 had complicated appendicitis. Younger age, duration of illness as well as vomiting, diarrhea, and fever were more common in complicated than uncomplicated appendicitis. White blood cell count, neutrophil count and C-reactive protein were higher in complicated appendicitis. Logistic regression showed that vomiting and presence of fever occurred more frequently in children with non-perforated gangrenous appendicitis than with other uncomplicated appendicitis. Laboratory results for non-perforated gangrenous appendicitis were comparable to those of complicated appendicitis, as was usage of radiography and computed tomography.

Conclusions: Gangrenous appendicitis shares similar historical elements with complicated appendicitis and has a similar laboratory. These children, like those with complicated appendicitis, may not be optimal candidates for non-operative management.

IMAJ 2026; 28: 93–98

KEY WORDS: appendicitis, gangrene, pediatric, laboratory

Gangrenous appendicitis is the midpoint of the continuum between uncomplicated and complicated appendicitis. Gangrene compromises the integrity of the appendiceal wall, but the wall remains macroscopically intact. Some researchers classify gangrene as complicated [1,2] while others consider gangrenous appendicitis to be uncomplicated [3]. The objective of our study is to analyze the presentation of gangrenous appendicitis in our population.

The most current guidelines from the Society of American Gastrointestinal and Endoscopic Surgeons suggest that both adult and pediatric patients with complicated appendicitis should be managed operatively [4]. With non-operative management (NOM), a viable alternative to surgery in uncomplicated appendicitis, it becomes increasingly important to differentiate uncomplicated from complicated appendicitis preoperatively.

We present an 8-year single-center retrospective review of presentation, laboratory values, and surgical and pathological findings in uncomplicated, complicated, and gangrenous appendicitis. First, we identified preoperative historical and laboratory characteristics of complicated versus uncomplicated appendicitis in our population. Second, we reviewed all cases of gangrenous appendicitis to better understand whether the presentation of gangrenous appendicitis is more similar to other complicated or other uncomplicated appendicitis in our population. Our results form the basis for prospective study to maximize the success of NOM in uncomplicated appendicitis.

PATIENTS AND METHODS

This retrospective chart review was conducted at a tertiary care pediatric emergency department (PED with

27,000 visits annually. We used keyword searches of our facility's electronic medical records (Chameleon, Elad Health, Tel Aviv) to identify all children ages 0–18 years treated at the PED or any inpatient unit and diagnosed with appendicitis or periappendiceal abscess. We also included patients who underwent appendectomy from June 2016 to June 2024. Incidental and interval appendectomies were excluded. We defined complicated appendicitis as perforation or abscess formation on histological report or computed tomography (CT), peritonitis, on histological report or evidence of perforation (i.e., free appendicolith or perforated appendiceal lumen), abscess or peritonitis on surgical report. Gangrenous appendicitis was described as such on the pathology report. The variables reviewed included date, time, and duration of the PED visit, presenting symptoms, laboratory and imaging results, PED treatment, and surgical and pathology reports. Fever was reported as both a categorical and a nominal variable. Fever was recorded as the maximum temperature measured by any care provider in a febrile patient prior to PED presentation and was separately recorded as any tactile fever reported by the care provider prior to PED presentation. Ultrasound was the first imaging option for all cases concerning appendicitis. The accuracy of our ultrasound in diagnosing or grading appendicitis was not studied and is therefore not reported. CT was used as a secondary examination in cases of diagnostic uncertainty.

Patient consent was not required for this retrospective chart review (KMC 0202-23).

STATISTICAL ANALYSIS

Categorical and nominal variables were reported by prevalence and percentages. Continuous variables were reported as medians and IQR when abnormal distribution was found between the various study groups by Shapiro- Wilk test. Categorical and nominal variables were analyzed by Pearson's chi-square test or Fisher exact test. A *P*-value < 0.05 was considered statistically significant.

We conducted the Kruskal-Wallis rank sum test with Bonferroni correction for multiple comparisons to evaluate the differences among groups while controlling for the risk of Type I errors due to multiple testing. Multiple logistic regression analysis was conducted to identify predictors of gangrenous and separately of complicated appendicitis. C-reactive protein (CRP) was analyzed as a continuous predictor and regression models calculated odds ratios per 1 mg/dl increase. The model discrimination was evaluated with C-statistics, calculated from the receiver operating characteristic curve of the predicted probabilities of gangrenous and of complicated appendicitis. High discrimination represents high sensitivity and specificity of the test.

Subsequently, for each group (gangrenous, complicated, and their combination), we performed logistic regression in comparison to children without gangrene

Figure 1. Logistic regression tables for complicated appendicitis presenting odds ratios with corresponding *P*-values

*_P_-value < 0.05

**_P_-value < 0.01

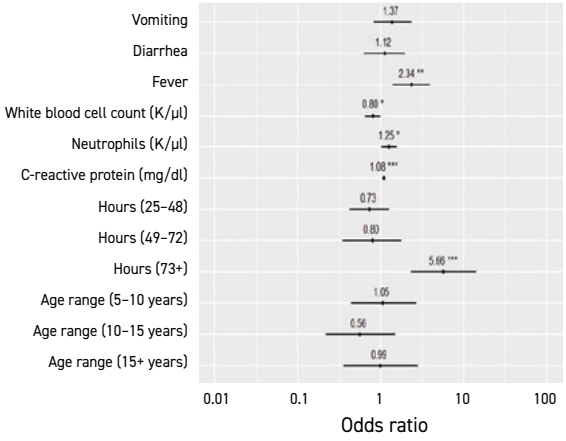
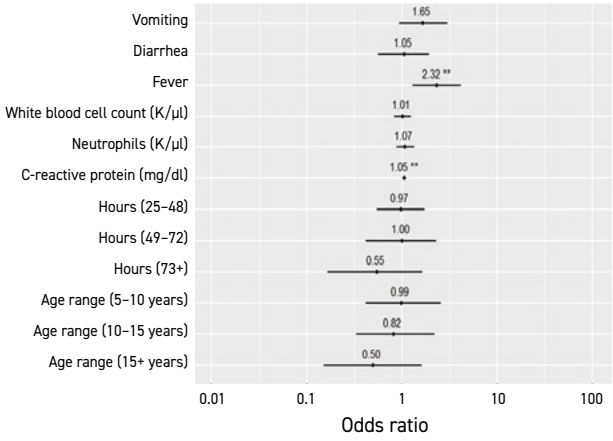


Figure 2. Logistic regression tables for gangrenous appendicitis presenting odds ratios with corresponding *P*-values

*_P_-value < 0.05

**_P_-value < 0.01



and without complications. The regression included all variables that were significant in the multiple comparison analysis, except for variables that demonstrated multicollinearity with others. The area under the curve (AUC) and lower and upper 95% confidence interval (95%CI) were calculated, as well as the test parameters, including: sensitivity, specificity. A lower 95%CI > 0.5 was considered significant.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 27 (SPSS, IBM Corp, Armonk, NY, USA) and R Statistical Software, version 4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 999 children were diagnosed with appendicitis. Of the 999 children, 126 without signs of complicated appendicitis were treated nonoperatively and excluded from regression analyses. In total, 739 chil-

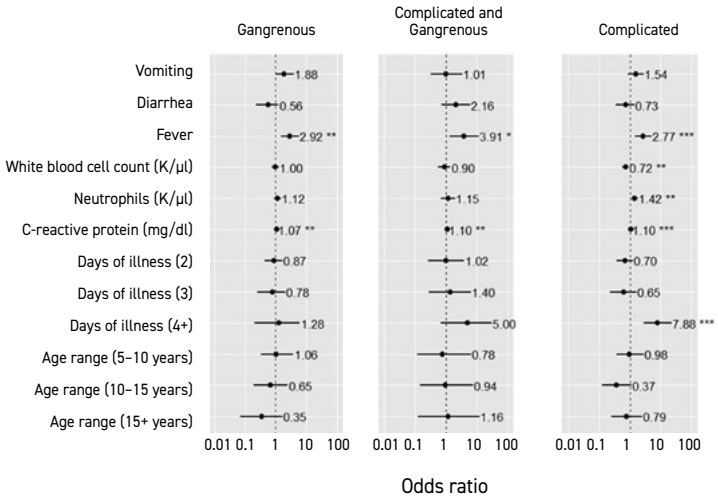


Figure 3. Multiple comparisons, appendicitis that is uncomplicated and not gangrenous compared with appendicitis that is complicated, appendicitis that is gangrenous and appendicitis that is both

*P-value < 0.05

**P-value < 0.01

Table 1. Gangrenous, non-gangrenous, complicated, and uncomplicated appendicitis

Variable	N=999	Not complicated and gangrenous (n=73), n (%)	Not complicated and not gangrenous (n=666), n (%)	Complicated and gangrenous (n=22), n (%)	Other complicated appendicitis (n=112), n (%)	Treated non-operatively (n=126), n (%)	*P*-value*
Age range in years							< 0.001
0–5		6 (8.2%)	22 (3.3%)	4 (18%)	15 (13%)	4 (3.2%)	
5–10		36 (49%)	223 (33%)	6 (27%)	49 (44%)	30 (24%)	
10–15		25 (34%)	305 (46%)	9 (41%)	31 (28%)	40 (32%)	
15+		6 (8.2%)	116 (17%)	3 (14%)	17 (15%)	52 (41%)	
Two PED visits	999	5 (6.8%)	18 (2.7%)	2 (9.1%)	6 (5.4%)	2 (1.6%)	0.048
Days of illness at presentation, median (IQR)	999	2 (1–2)	1 (1–2)	2 (2–3)	2 (1–3)	1 (1, 2)	< 0.001
Vomiting	999	57 (78%)	353 (53%)	16 (73%)	81 (72%)	53 (42%)	< 0.001
Diarrhea	999	12 (16%)	99 (15%)	11 (50%)	27 (24%)	28 (22%)	< 0.001
Fever	999	29 (40%)	95 (14%)	14 (64%)	57 (51%)	27 (21%)	
White blood cell count (K/µl), median (IQR)	999	17.7 (14.5–21.9)	14.6 (11.6–17.6)	15.9 (12.0–20.8)	16.4 (12.9–19.2)	13.5 (10.4–16.1)	< 0.001
Neutrophils (K/µl), median (IQR)[3]	999	14.4 (12.1–19.4)	11.6 (8.6–14.8)	13.6 (10.3–16.9)	13.6 (10.6–16.3)	10.4 (7.3–13.4)	< 0.001
C-reactive protein (mg/dl), median (IQR)**	872	6.2 (2.1–11.7)	1.4 (0.4–4.4)	13.6 (3.8–21.2)	7.0 (2.3–15.9)	1.1 (0.2–4.3)	< 0.001
Chest X-ray	999	14 (19%)	74 (11%)	5 (23%)	24 (21%)	13 (10%)	0.007
Computed tomography	999	12 (16%)	57 (8.6%)	6 (27%)	21 (19%)	19 (15%)	< 0.001
Fecalith	999	8 (11%)	44 (6.6%)	8 (36%)	20 (18%)	3 (2.4%)	< 0.001

*Pearson's chi-square test, Fisher's exact test, Kruskal-Wallis rank sum test

**Denominators for C-reactive protein are, from left column to right column: 65, 581, 22, 97, 107

IQR = interquartile range, PED = pediatric emergency department

dren treated operatively had uncomplicated appendicitis and 134 had complicated appendicitis.

Logistic regression showed that fever, white blood cell count (WBC), neutrophil count, CRP, and presentation on day 4 of illness were all predictive of complicated appendicitis [Figure 1] with an AUC of 0.79. In multivariable analysis, CRP was independently associated with complicated appendicitis (adjusted odds ratio [OR] 1.09, 95%CI 1.05–1.13, $P < 0.001$). That is, every unit increase in CRP increased the risk of complicated appendicitis by 9%. Only fever and CRP predicted gangrenous appendicitis. Every unit increase in CRP increased the risk of gangrenous appendicitis by 5%, and patients presenting with fever had a 2.3-time greater risk of gangrenous appendicitis than children presenting afebrile [Figure 2].

We then evaluated gangrenous appendicitis with and without signs of complication [Table 1] to determine whether each of these two entities presented more similarly to all uncomplicated or to all uncomplicated appendicitis in our population. There were 95 cases of gangrenous appendicitis, of which 73 were without signs of complication on pathology. In 73 of the 95 cases (77%) of gangrenous appendicitis as identified on pathology report, the gangrene was noted in the operative report as well. In 12 cases (13%) the operative report noted neither gangrene nor any other sign of complication.

Vomiting and presence of fever, which were associated with complicated appendicitis, occurred more frequently in children with non-perforated gangrenous appendicitis than with other uncomplicated appendicitis. WBC and CRP levels in non-perforated, gangrenous appendicitis were comparable to those of complicated appendicitis rather than to non-gangrenous non-perforated appendicitis [Table 1]. CT rates in non-perforated, gangrenous appendicitis were 16% versus 19% in other complicated appendicitis. Thus, nonperforated, gangrenous appendicitis appears to be closer on the spectrum of severity to complicated appendicitis than to uncomplicated, non-gangrenous appendicitis.

CRP and fever were significant predictors for gangrenous appendicitis in all three regression models [Figure 3]. Univariate regression analyses were conducted to evaluate their individual contributions and to determine optimal CRP thresholds for predicting disease severity. At a CRP cutoff of 3 mg/dl, the ability to distinguish gangrenous appendicitis showed AUC = 0.67 (95%CI 0.61–0.74), sensitivity 0.68, and specificity 0.67. For complicated appendicitis, performance improved slightly (AUC = 0.72, sensitivity 0.77, specificity 0.67). For both severe categories combined, AUC was 0.68. A CRP cutoff of 4 mg/dl yielded comparable accuracy (AUC = 0.65 for gangrenous, 0.73 for complicated, 0.67 overall), with a trade-off of lower sensitivity (0.58) but higher specificity (0.72) for gangrenous cases.

Taken together, a 3 mg/dl CRP threshold provides a balanced trade-off between sensitivity and specificity for identifying complicated or gangrenous appendicitis, while 4 mg/dl prioritizes specificity and may be useful when minimizing false positives is a priority.

DISCUSSION

We found that fever, elevated laboratory values, and delayed presentation were predictive of complicated appendicitis, which is similar to other study results [5]. Moreover, fever, vomiting, and laboratory profile in gangrenous appendicitis without intraoperative or histologic signs of complication more closely resemble markers of complicated rather than uncomplicated appendicitis. Gangrenous uncomplicated appendicitis, like complicated appendicitis, was associated with greater use of radiography and CT than uncomplicated appendicitis [Table 1], perhaps indicating an increase in diagnostic uncertainty compared with other uncomplicated appendicitis.

The World Society of Emergency Surgery Jerusalem guidelines for the treatment of acute appendicitis state that NOM, in the absence of fecalith, is a "safe and effective alternative to surgery in children with uncomplicated acute appendicitis" [6]. A recent meta-analysis in the pediatric population showed that perforated appendicitis is best treated operatively, while appendiceal abscess is best treated non-operatively [7]. Studies of NOM for pediatric appendicitis were conducted retrospectively, or children were randomly assigned to a NOM arm [8]. Failure rates for NOM can approach 30% at 90 days [9] and 39% at 5 years [10]. Thus, exclusion of early complications such as gangrene from NOM studies may optimize the success of NOM as a treatment strategy for uncomplicated pediatric appendicitis.

Several authors studied gangrenous appendicitis postoperatively and found similarities to uncomplicated appendicitis. Shbat et al. [11] allocated 58 patients with gangrenous appendicitis to prolonged or abridged postoperative antibiotic treatment arms and found no difference in outcomes between groups. Similarly, Nordin

and colleagues [3] placed gangrenous appendicitis in the postoperative antibiotic protocol for uncomplicated appendicitis and found no increase in complications and a decrease in length of hospitalization for children with gangrenous appendicitis.

Several authors have demonstrated that gangrene is identifiable on ultrasound and that loss of the submucosal layer of the appendix and transmural necrosis are predictive of complicated appendicitis [12,13]. Levy and colleagues [14] showed that mucosal ulceration on sonography increased the odds of failure of conservative treatment by a factor of 7.3, while intact mucosa had a negative predictive value of 91% for successful conservative management. Dessie et al. [15] showed that pediatric emergency physicians could distinguish between uncomplicated (Puylart stage 1 and two) and complicated (Puylart stage 3 or 4) appendicitis with a sensitivity of 100% and a specificity of 64% in an average of 8 minutes. Nijssen and co-authors [16] studied 176 children and found only 46% sensitivity with 90% specificity for the sonographic diagnosis of complicated appendicitis and concluded that ultrasonography alone is not sufficient for differentiating between simple and complicated appendicitis in children.

Improvement in ultrasound technology and incorporation of sonographic scoring may be the next step in building prediction models to optimize the success of NOM. However, our study argues that gangrenous appendicitis, despite the intact appendiceal wall, presents more closely to complicated appendicitis, and therefore the sonographic integrity of the appendiceal wall alone (assuming no fecalith) should not be the only criteria in determining eligibility for conservative care. Particularly as ultrasound quality and training improves to the point where more routine identification of areas of gangrene is possible, sonographic findings concerning for gangrene may warrant exclusion of that child from NOM protocols.

While prior literature has developed decision rules incorporating history, physical examination and laboratory values that risk-stratify a diagnosis of pediatric appendicitis do not distinguish between complicated and uncomplicated disease [17]. Several authors have correlated higher inflammatory markers with more severe disease [18,19]. However, no studies have allocated pediatric patients prospectively into NOM or surgical arms based on clinical or laboratory cutoffs validated to predict appendicitis grade. Laboratory and/or sonographic guidelines that predict uncomplicated versus complicated appendicitis would be critical in risk-stratifying pediatric patients with appendicitis for operative or non-operative care. The validation of the SAS 2.0 tool to risk-stratify complicated appendicitis in adults included gangrene without intraoperative evidence of appendiceal wall necrosis as a complication [20].

We are not aware of prior pediatric studies focused specifically on preoperative presentation of gangrenous appendicitis. In the absence of clear guidelines directing NOM in children, our study is a building block in the process of defining optimal exclusion criteria for NOM. Our study demonstrates that gangrene without frank perforation presents similarly to complicated appendicitis in children and may warrant exclusion from NOM treatment protocols. Future studies should focus on the sonographic markers of gangrenous appendicitis and evaluate the efficacy of conservative management in cases of suspected uncomplicated appendicitis based on laboratory testing and presence of appendiceal necrosis on imaging evaluation.

LIMITATIONS

In this retrospective study, physical examination was variably reported. Therefore, we did not collect physical examination data or retrospectively use a scoring algorithm for appendicitis. CRP was not routinely collected until 2018, and the percentages reported in the tables are percentages of values recorded. From the age of 15 years, children are treated by general surgeons who have an increased preference for conservative therapy than our pediatric surgeons. We could not assess the extent of the gangrene, whether mucosal or transmural, from the pathology report. As gangrene is an advanced stage in the spectrum of appendiceal inflammation, we cannot determine whether gangrene was present at the time of laboratory assessment or developed in the interim between assessment and surgery. Given that a visual operative assessment of appendicitis severity is a less rigorous standard than the pathology examination, we used only the pathology examination to identify gangrenous appendicitis.

CONCLUSIONS

Gangrenous appendicitis shares similar historical and laboratory characteristics with complicated appendicitis. Children with gangrenous appendicitis may not be optimal candidates for NOM and, as with other complicated appendicitis, are better treated surgically.

Acknowledgments

The authors thank their statisticians, Merav Greenstein and Ronit Harris, for their work on this project.

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References

1. Gomes CA, Nunes TA, Fonseca Chebli JM, et al. Laparoscopy grading system of acute appendicitis: new insight for future trials. *Surg Laparosc Endosc Percutan Tech* 2012; 22 (5): 463-6.
2. Gorter RR, van den Boom AL, Heij HA, et al. A scoring system to predict the severity of appendicitis in children. *J Surg Res* 2016; 200 (2): 452-9.
3. Nordin AB, Diefenbach K, Sales SP, et al. Gangrenous appendicitis: no longer complicated. *J Pediatr Surg* 2019; 54 (4): 718-22.
4. Kumar SS, Collings AT, Lamm R, et al. SAGES guideline for the diagnosis and treatment of appendicitis. *Surg Endosc* 2024; 38 (6): 2974-94.
5. van den Bogaard VA, Euser SM, van der Ploeg T, et al. Diagnosing perforated appendicitis in pediatric patients: a new model. *J Pediatr Surg* 2016; 51 (3): 444-8.
6. Di Saverio S, Podda M, De Simone B, Ceresoli M, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg* 2020; 15 (1): 27.
7. Fugazzola P, Coccolini F, Tomasoni M, et al. Early appendectomy vs. conservative management in complicated acute appendicitis in children: a meta-analysis. *J Pediatr Surg* 2019; 54 (11): 2234-41.
8. Hall NJ, Eaton S. Non-operative management of appendicitis in children. *Arch Dis Child* 2018; 103 (5): 498-502.
9. Talan DA, Saltzman DJ, DeUgarte DA, Moran GJ. Methods of conservative antibiotic treatment of acute uncomplicated appendicitis: a systematic review. *J Trauma Acute Care Surg* 2019; 86 (4): 722-36.
10. Salminen P, Tuominen R, Paajanen H, et al. Five-year follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial. *JAMA* 2018; 320 (12): 1259-65.
11. Shbat L, Emil S, Elkady S, et al. Benefits of an abridged antibiotic protocol for treatment of gangrenous appendicitis. *J Pediatr Surg* 2014; 49 (12): 1723-5.
12. Rawolle T, Reismann M, Minderjahn MI, et al. Sonographic differentiation of complicated from uncomplicated appendicitis. *Br J Radiol* 2019; 92 (1099): 20190102.
13. Xu Y, Jeffrey RB, Chang ST, DiMaio MA, Olcott EW. Sonographic differentiation of complicated from uncomplicated appendicitis: implications for antibiotics-first therapy. *J Ultrasound Med* 2017; 36 (2): 269-77.
14. Levy S, Hiller N, Lev-Cohain N, Goldberg SN, Mizrahi I, Simanovsky N. Ultrasonographic features can predict outcome of conservative management of acute appendicitis in children. *Emerg Radiol* 2022; 29 (1): 59-65.
15. Dessie AS, Kwok M, Mills L, et al. Prospective observational study of emergency department point-of-care ultrasound to differentiate between complicated and uncomplicated appendicitis. *J Ultrasound Med* 2025; 44 (8): 1473-80.
16. Nijssen DJ, van Amstel P, van Schuppen J, Eeftinck Schattenkerk LD, Gorter RR, Bakx R. Accuracy of ultrasonography for differentiating between simple and complex appendicitis in children. *Pediatr Surg Int* 2021; 37 (7): 843-9.
17. Fawkner-Corbett D, Hayward G, Alkhmees M, et al. Diagnostic accuracy of blood tests of inflammation in paediatric appendicitis: a systematic review and meta-analysis. *BMJ Open* 2022; 12 (11): e056854.
18. Li X, Gong S, Ding Y, et al. Preoperative inflammatory markers in pediatric appendicitis: associations with disease severity, postoperative recovery, pain, and surgical outcomes. *BMC Pediatr* 2025; 25 (1): 597.
19. Gorter RR, van den Boom AL, Heij HA, et al. A scoring system to predict the severity of appendicitis in children. *J Surg Res* 2016; 200 (2): 452-9.
20. Scheijmans JCG, Bom WJ, Ghori UH, et al. Development and validation of the Scoring System of Appendicitis Severity 2.0. *JAMA Surg* 2024; 159 (6): 642-9.

Capsule

Antitumor combination therapy

Tumor antigen vaccines have been considered a promising approach to cancer treatment but have struggled to progress due to limited efficacy. **Hwang** et al. followed a cohort of surviving breast cancer patients vaccinated approximately 18 years ago with a human epidermal growth receptor 2^{+} (HER^{2+})-targeting dendritic cell-based vaccine. These patients all had HER2-specific $CD27^{+}$ memory CD4 and CD8 T cells in their peripheral blood, suggesting the presence of a specific subset of long-lived memory T cells. Further analysis in transgenic mice expressing human CD27 confirmed that primary HER2 vaccination combined with an agonistic anti-CD27 monoclonal antibody enhanced antitumor responses, especially in combination with anti-PD1 antibody treatment. CD4 T cells were the critical cell type for orchestrating antitumor responses. These results highlight the potential benefit of tumor vaccines combined with CD27 agonism.

Sci Immunol 2025; 10 (114): eadz2294
Eitan Israeli