

More isn't always better: antibiotic duration after surgical decortication in pleural empyema

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Background: While ample high-level evidence supports the limited use of antibiotics post-source control in intraabdominal infections, there is a paucity of available data in guiding antibiotic duration for intrathoracic infections. This study aims to analyze patient outcomes among those who have undergone surgical decortication for parapneumonic pleural empyema, comparing cases managed with infectious disease (ID) specialists against those without, and to identify predictive factors influencing antibiotic duration post-source control. We hypothesized that antibiotic duration would vary depending on the involvement of ID specialists.

Methods: A retrospective chart review was completed on patients with parapneumonic pleural empyemas who underwent surgical decortication at a single tertiary center from January 2011 to March 2021. Differences in patient characteristics and outcomes for those whose antibiotics were managed by ID or not were compared with Wilcoxon two-sample tests and Fisher's exact tests. Linear regression was used to evaluate for significant factors predictive of antibiotic duration.

Results: A total of 116 patients underwent surgical decortication for pleural empyema of parapneumonic etiology. ID specialists were involved with antibiotic management in 62 (53.4%) cases, while the remaining cases were not managed by ID. Demographics and patient comorbidities were similar between both groups. Growth of preoperative fluid cultures was higher in patients managed by ID (40.3% *vs.* 20.4%, P=0.03). Postoperatively, patients managed by ID had longer durations of antibiotics (28.7 *vs.* 20.9 days, P<0.001) and were more likely to be on IV antibiotics than patients not managed by ID (59.7% *vs.* 38.9%, P=0.04). However, postoperative outcomes were similar, including rates of disease recurrence, readmission, and 30-day mortality. Linear regression revealed length of antibiotics was significantly dependent on preoperative ventilator status [estimate: 16.346; 95% confidence interval (CI): 6.365–26.326; P=0.002], growth of preoperative pleural fluid cultures (estimate: 10.203; 95% CI: 2.502–17.904; P=0.01), and ID involvement (estimate: 8.097; 95% CI: 1.003–15.191; P=0.03).

Conclusions: Antibiotic duration for pleural empyema managed with surgical decortication is significantly dependent on ID involvement, preoperative growth of cultures, and preoperative ventilator status. However, outcomes, including disease recurrence and 30-day mortality, were similar between patients regardless of ID involvement and longer length of antibiotics, raising the question of what the adequate duration of antibiotics is for patients who receive appropriate source control for pleural empyema. Further study with randomized control trials should be conducted to provide high-level evidence regarding length of antibiotics in this patient population.

Keywords: Pleural empyema; antibiotics; surgical decortication; thoracic surgery

Submitted Jan 10, 2024. Accepted for publication Apr 24, 2024. Published online Jun 13, 2024. doi: 10.21037/jtd-24-61

View this article at: https://dx.doi.org/10.21037/jtd-24-61

Introduction

Approximately 32,000 cases of pleural empyema are diagnosed each year in the United States (1). Despite this level of incidence, mortality remains high with a reported 5% to 20% mortality rate (1-3). The treatment and management of pleural empyema is challenging, typically requiring a multidisciplinary approach of multiple medical and surgical specialties including pulmonology, infectious disease (ID), and thoracic surgery (1,4,5). If the diagnosis of empyema is suspected or confirmed, management commences with the prompt initiation of antibiotics and drainage of the infected pleural fluid. Empiric antibiotic initiation typically includes an antibiotic targeting anaerobic bacteria with additional antibiotics based on the suspected associated cause (community-acquired pneumonia, hospitalacquired pneumonia, aspiration, trauma, etc.), with directed therapy then used based on results from the cultured pleural fluid (6). In addition to early initiation of antibiotics, prompt drainage is indicated in cases of empyema to obtain source control (7). Initial drainage procedure can be completed with single tube thoracostomy. Intrapleural fibrinolytics,

Highlight box

Key findings

 Longer durations of antibiotics did not result in better clinical outcomes for patients with pleural empyema treated with surgical decortication.

What is known and what is new?

- The treatment of pleural empyema is complicated by a lack of evidence regarding the appropriate length of antibiotic therapy after adequate source control.
- Our study helps to better characterize antibiotic management in patients undergoing surgical decortication for pleural empyema and questions whether antibiotics are being overused in the treatment of pleural empyema after source control has been obtained.

What is the implication, and what should change now?

 It is now time for the management of pleural empyema to modernize and to be driven by high-level evidence regarding antibiotic therapy. The completion of randomized control trials is warranted and needed to better understand the optimal duration of antibiotics for pleural empyemas requiring surgical intervention. including tissue plasminogen activator and DNase, can be added to the management algorithm to assist in the breakdown of septations and loculations thereby improving drainage (8). However, 30–40% of patients with empyema require escalation of therapy with definitive source control via thoracoscopic or open surgical decortication (1,6,9).

Despite this already complex management, the treatment of pleural empyema is further complicated by a lack of evidence regarding the appropriate length of antibiotic therapy after adequate source control (i.e., drainage with or without lytic therapy, or surgical decortication). This clinical dilemma is aptly juxtaposed by the current management of antibiotics in intraabdominal infections. The publication of the landmark "STOP-IT" randomized control trial revolutionized the management of antibiotic therapy after source control for intraabdominal infections. The trial showed that shorter durations of antibiotics (i.e., 4 days) compared to longer durations of antibiotics (i.e., 8 days) had similar outcomes after adequate source control was performed (10). Unfortunately, no such high-level or randomized control data exists for pleural empyemas after adequate source control. As such, antibiotic duration after source control varies greatly with literature reporting continuation of antibiotics for 2-6 weeks (1). Longer durations of antibiotics are not without their own side effects and complications specific to their pharmacologic profiles and modes of administration (11,12).

The development of antibiotic resistance has become a major public health issue. Multidrug-resistant bacteria are associated with increased mortality and prolonged hospital length of stay (13,14). The Center for Disease Control reports 20% to 50% of antibiotics prescribed in United States hospitals are unnecessary or inappropriate (15). With the proper utilization of antibiotics being at the forefront of healthcare, health systems have adopted antimicrobial stewardship programs to coordinate the optimization of antimicrobial usage. These programs center around selecting the correct antimicrobial agent and its appropriate dosing, route of administration, and duration. These pivotal efforts are led by ID physicians along with ID-specialized pharmacists (16). Undoubtedly, pleural empyema is one such ID that often requires the consultation of ID physicians in helping manage and dictate antibiotic therapy.

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Cohort data has shown that 3 weeks of antibiotics was adequate after surgical management for pleural empyema, but this data is limited by its sample size and retrospective, non-randomized data (17). Similarly, in 2010, the British Thoracic Society Guidelines recommended at least 3 weeks of antibiotics (4). The 2017 American Association of Thoracic Surgery (AATS) Empyema Management Guidelines Working Group recommended a minimum of 2 weeks of antibiotic therapy after source control and defervescence with a rating of Level C class evidence (e.g., recommendation based on expert opinion, case studies, or standard-of-care) (1). This lack of high-quality evidence underscores the need for further investigation into antibiotic duration after source control for pleural empyemas.

Given this, we elected to perform a single institution retrospective chart review of patients diagnosed with pleural empyema and treated with surgical decortication to better characterize antibiotic duration and outcomes. From our clinical experience, it was hypothesized that ID involvement in antibiotic management results in longer durations of antibiotics than cases where ID was not involved, presenting a dichotomous cohort for comparison. This comparison was generated in order to create two separate groups with likely differing styles of antibiotic management in terms of length of duration and route of administration that we could easily compare. As such, in this study, we aimed to (I) compare outcomes for patients with parapneumonic pleural empyemas treated with surgical decortication whose antibiotic therapy was managed by ID specialists or not, and (II) determine what clinical factors are associated with longer postoperative antibiotic duration. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/ view/10.21037/jtd-24-61/rc).

Methods

Patient selection & clinical data

A retrospective chart review was completed for all patients who underwent surgical decortication for pleural empyema at a single tertiary center from January 2011 to March 2021. Patients were identified for having undergone intrathoracic surgical decortication and each patient's medical record was independently reviewed to ensure the indication of the surgery was for pleural empyema. Patients were included if they were 18-89 years old, underwent surgical decortication for pleural empyema and had empyema of parapneumonic

including empyemas secondary to trauma, septic emboli, etc., and patients who were on antibiotics for reasons other than pleural empyema during their treatment course were excluded from this study to minimize confounding factors in assessing antibiotic duration. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board (IRB) at Virginia Commonwealth University (No. HM20021602) and informed consent was waived for this retrospective analysis.

Clinical data collected from each patient's medical record included patient demographics, comorbid risk factors, preoperative management, and intraoperative and postoperative outcomes. Demographics included age, sex, race, body mass index (BMI), and insurance status (private or government-based paver). Risk factors included the presence of diabetes mellitus, congestive heart failure, chronic kidney disease, cardiovascular disease, chronic obstructive pulmonary disease (COPD), history of tobacco use, and current tobacco use. Preoperative factors included placement of a chest thoracostomy tube, obtainment of preoperative pleural fluid cultures, growth of preoperative fluid cultures, and the patient's oxygenation status (e.g., on room air, on nasal canula, or on a ventilator). Intraoperative factors included the surgical approach [e.g., open thoracotomy, video-assisted thoracoscopic surgery (VATS), vs. conversion from VATS to open] and growth of intraoperative pleural cultures. Postoperative outcomes included complications within 30 days of surgery such as need for blood transfusion, reoperation, reintubation, tracheostomy, prolonged air leak (defined as an air leak >5 days), readmission within 30 days of discharge, and empyema recurrence (defined as evidence of recurrence on imaging or needing additional intervention for control). Lastly, antibiotic duration from the time of source control (i.e., surgery) to completion and the antibiotic route (oral vs. intravenous) of completion were recorded.

Statistical analysis

Data were stratified by whether patient's antibiotics were or were not managed by ID specialists. Differences between these groups for patient demographics, management, and outcomes were compared with Wilcoxon Rank two-sample tests for continuous variables and Fisher's exact tests for categorical variables. Predictors of antibiotic duration were determined as parameter estimates using linear regression

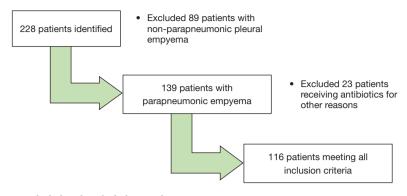


Figure 1 Schematic of patients included and excluded in study.

with stepwise selection including only the factors with a P value less than 0.2 from univariate analysis. All tests were two-sided and an alpha level of 0.05 was used for determining statistical significance. All statistical analyses were conducted in SAS version 9.4 (Cary, NC, USA).

Results

Initially, 228 patients were identified as having undergone surgical decortication for pleural empyema. Of these, only 116 (50.9%) patients with parapneumonic pleural empyemas were included in the final analysis for meeting all inclusion criteria (*Figure 1*).

Patient characteristics

Nearly half of these patients (53.4%, n=62) received postoperative antibiotic management by ID specialists, while the remaining patients had their antibiotics managed by non-ID specialists (e.g., thoracic surgery, internal medicine, pulmonology) (Table 1). There was no difference in patient age, sex, BMI, race, or insurance payer when comparing cohorts by ID involvement. Additionally, the incidence of comorbid conditions such as diabetes, congestive heart failure, chronic kidney disease, and cardiovascular disease were similar between both groups. Patients managed by ID had higher rates of COPD (53.2%) compared to those not managed by ID (40.7%), though this was not statistically significant (P=0.20). Almost two-thirds (62.9%) of all patients reported a positive history of tobacco use with 38.8% of all patients being current tobacco smokers. This did not vary between groups. The preoperative white blood cell count was similar between patients who received an ID consultation and those who did not $(14.2 \times 10^9/L vs.)$

 14.2×10^{9} /L, P=0.95). Initial management with obtaining pleural fluid cultures and tube thoracostomy placement were similar between groups. The ID-managed group, however, had higher rates of positive preoperative culture growth compared to non-ID-managed patients (40.3% vs. 20.4%, P=0.03). Lastly, there was no difference between groups for preoperative oxygenation status of being on room air vs. requiring mechanical ventilation.

Intraoperative and postoperative outcomes

Intraoperative and postoperative outcomes stratified by group are presented in Table 2. There was no difference by group for surgical approach with similar rates of VATS vs. open vs. conversion of VATS to open. Additionally, complication rates were similar between these patient groups, specifically with respect to postoperative blood transfusion, prolonged air leak, reintubation, reoperation, and tracheostomy. There was also no difference in rates of readmission, recurrence, or 30-day mortality between groups. Interestingly, patients whose antibiotics were managed by ID received a significantly longer duration of antibiotics than patients who did not have ID involvement (28 vs. 15 days, P<0.001). Patients who were managed by ID were significantly more likely to be treated exclusively with intravenous (IV) antibiotics, rather than transitioning to oral antibiotics, in comparison to patients not managed by ID (IV: 59.7% vs. 38.9%, oral: 40.3% vs. 61.1%, P=0.04).

Determinants of antibiotic duration

To explore whether certain clinical variables influenced the length of antibiotic treatment independent of ID consultation, a post-hoc analysis was conducted (Table S1).

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Patient characteristics	Non-ID-managed (n=54)	ID-managed (n=62)	P value
Age (years)	53.9 (43.4–64.4)	56.3 (45.8–64.7)	0.66
BMI (kg/m²)	26.6 (22.9–33.4)	26.1 (23.2–30.1)	0.54
Sex			0.84
Male	38 (70.4)	45 (72.6)	
Race			0.45
White	29 (53.7)	36 (58.1)	
Black	20 (37.0)	24 (38.7)	
Other	5 (9.3)	2 (3.2)	
nsurance			>0.99
Private	18 (33.3)	21 (33.9)	
Government-based	24 (44.4)	28 (45.2)	
Uninsured	12 (22.2)	13 (21.0)	
Diabetes	11 (20.4)	14 (22.6)	0.82
Congestive heart failure	6 (11.1)	11 (17.7)	0.43
Chronic kidney disease	6 (11.1)	12 (19.4)	0.31
Cardiovascular disease	10 (18.5)	13 (21.0)	0.82
COPD	22 (40.7)	33 (53.2)	0.20
listory of tobacco use	31 (57.4)	42 (67.7)	0.34
Active smoker	22 (40.7)	23 (37.1)	0.71
Preoperative chest tube	23 (42.6)	25 (40.3)	0.85
Preoperative pleural fluid culture obtained	29 (53.7)	31 (50.0)	0.71
Pleural fluid culture growth	11 (20.4)	25 (40.3)	0.03
Preoperative WBC (×10 ⁹ /L)	14.2±7.13	14.2±7.04	0.95
Dn room air	22 (40.7)	20 (32.3)	0.44
On ventilator	10 (18.5)	8 (12.9)	0.45

Table 1 Patient characteristics for	those whose antibiotics were or	were not managed by ID specialists
	those whose antibiotics were of	were not managed by 1D specialists

Demographics, risk factors, and preoperative management for patients with parapneumonic empyemas that underwent surgical decortication. Continuous variables are represented as median (interquartile range) or mean ± SD, and categorical variables as number (percentage). ID, infectious disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; SD, standard deviation.

This analysis examined demographic and various preoperative, intraoperative, and postoperative factors in relation to antibiotic duration. It was found that patients with diabetes mellitus experienced a significantly longer antibiotic duration (34 *vs.* 23 days, P=0.04), as did those with positive preoperative cultures (31 *vs.* 22 days, P=0.03), and those requiring preoperative ventilator support (39 *vs.* 22 days, P=0.03). Contrarily, a positive intraoperative

culture was surprisingly linked to a shorter duration of antibiotic use (24 vs. 25 days, P=0.04).

Furthermore, linear regression was employed to determine the clinical factors associated with antibiotic duration for all patients. In total four clinical factors were included in the final model and are presented as point estimates (*Table 3*). The presence of a patient requiring mechanical ventilation preoperatively [point estimate:

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Table 2 Intraoperative and	l postoperative outcomes for	patients whose antibiotics were or w	ere not managed by ID specialists
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Intraoperative and postoperative outcomes	Non-ID-managed (n=54)	ID-managed (n=62)	P value
Surgical approach			0.75
VATS	36 (66.7)	37 (59.7)	
VATS to open	10 (18.5)	15 (24.2)	
Open	8 (14.8)	10 (16.1)	
ntraoperative culture growth	24 (44.4)	38 (61.3)	0.09
Reoperation	5 (9.3)	4 (6.5)	0.73
Postoperative transfusion	14 (25.9)	21 (33.9)	0.42
Prolonged air leak	2 (3.7)	9 (14.5)	0.06
Discharged with chest tube	2 (3.7)	5 (8.1)	0.45
racheostomy	2 (3.7)	2 (3.2)	>0.99
Reintubation	2 (3.7)	7 (11.3)	0.17
Readmission	6 (11.1)	7 (11.3)	>0.99
Empyema recurrence	0 (0.0)	2 (3.2)	0.50
30-day mortality	1 (1.9)	3 (4.8)	0.62
Antibiotic duration (days)	15 [12–21]	28 [21–39]	<0.001
Antibiotic route			0.04
Oral	33 (61.1)	25 (40.3)	
IV	21 (38.9)	37 (59.7)	

Continuous variables are represented as median [interquartile range] and categorical variables as number (percentage). ID, infectious disease; VATS, video-assisted thoracoscopic surgery; IV, intravenous.

Table 3 Predictors of antibiotic duration

Clinical factors	Estimate	95% CI	P value
BMI	0.615	0.176-1.053	0.006
Preoperative ventilator	16.346	6.365–26.326	0.002
Preoperative pleural culture growth	10.203	2.502-17.904	0.01
ID consult	8.097	1.003–15.191	0.03

Clinical factors associated with antibiotic duration after surgical decortication as determined by linear regression for patients with parapneumonic pleural empyemas. CI, confidence interval; BMI, body mass index; ID, infectious disease.

16.346; 95% confidence interval (CI): 6.365-26.326; P=0.002] and having a positive pleural fluid culture preoperatively (point estimate: 10.203; 95% CI: 2.502–17.904; P=0.01) were both significant predictors of increased length of antibiotic therapy duration. Additionally, the involvement of ID in the management of the antibiotics was found to be a significant factor in antibiotic duration as its presence increased the total length of antibiotics by a

point estimate of 8.097 (95% CI: 1.003-15.191; P=0.03).

Discussion

Antibiotic management after surgical decortication for empyema is not standardized and lacks evidence-driven consensus, resulting in questions surrounding the optimal duration of antibiotics after source control. Although this study does not address determining optimal duration, which may be better determined by prospective, randomized control trials, we did show that longer durations of antibiotics did not result in better patient outcomes, including disease recurrence and 30-day mortality. Additionally, the duration of antibiotics after surgery was found to be dependent on whether the antibiotics were managed by ID specialists or not, an interesting finding. Again, this comparison was done to create patient groups likely to have differences in antibiotic management from institutional experience. These findings do not and are not to discredit the involvement of ID specialists, but again put forth the issue of how long patients should be on antibiotics after source control for pleural empyema.

There has been interest in this issue in pediatric pleural empyema research. When surveying physicians who treat parapneumonic pleural effusions and empyemas, such as surgeons, pulmonologists, intensivists, and interventional radiologists, Richards et al. (18), showed that there was substantial disagreement between the different specialties with respect to antibiotic duration and route. Of those surveyed, 58.8% of respondents stated that antibiotics should be continued until resolution of symptoms, while 36.9% of respondents believed antibiotics should be continued for a minimum number of days (17). With respect to the route of antibiotic administration, 33.5% of respondents believed transition from IV to oral antibiotics should occur after a specific number of days of IV treatment, 17.9% of respondents prescribed to a specific number of days of both IV and oral antibiotics, and 16.9% of respondents continued IV antibiotics until resolution of symptoms (18). In a 2019 study, when presented with two different clinical cases of empyema, the antibiotic prescribing practices of pediatric ID physicians varied (19). These data highlight the discordant practices of antibiotic therapy in the treatment of pleural empyema even amongst the many specialties involved in the treatment of this disease process, including ID physicians.

Lack of evidence-driven guidelines and protocols attribute to these varying practices. Svetanoff *et al.*, however, showed that antibiotic usage improved with standardized protocol. In this 2020 study, a new protocol was implemented for pediatric patients with pleural empyema treated with fibrinolysis, where seven days of additional antibiotics were prescribed after removal of the thoracostomy tube in a clinically improved patient. The mean duration of total antibiotics decreased significantly after implementation of the protocol and resulted in fewer days of antibiotics after discharge. Importantly, there were less antibiotic-related adverse effects with this new protocol and no difference in disease recurrence or readmission (20). Although this study was conducted in the pediatric population and is specific to source control via intrapleural fibrinolytics, not surgical decortication, these findings corroborate our results, suggesting that shorter durations of antibiotics may be as effective as a longer course of antibiotics in treating this patient population.

Similarly, a small randomized controlled study was conducted in Spain evaluating the length of duration of antibiotics for adult patients with complicated parapneumonic pleural effusions treated with thoracostomy drainage with or without intrapleural fibrinolytics, the Optimal Duration of Antibiotics in Parapneumonic Effusions (ODAPE) trial (21). Although with a small sample of 55 patients, the authors found no major difference in outcomes between patients treated with 2 vs. 3 weeks of antibiotics. This again suggests that lesser durations of antibiotics may be appropriate for the treatment of empyema, further corroborating our results.

When discussing antibiotic administration in the treatment of ID, it is also important to consider the route of administration. In our patient population, half of all patients completed their antibiotic course via IV antibiotics, with 63.8% (37/58) of these patients having their antibiotics managed by ID. IV antibiotics are not without their own risks stemming from the antibiotic itself to its delivery via a centrally-placed catheter. The potential to transition from IV to oral antibiotics is desired in the appropriate clinical context. The AATS recommends transition to oral antibiotics if clinical data is favorable for such (1). A retrospective review, again in the pediatric population, however, showed that an early transition from IV to oral antibiotics (4–6 days) resulted in favorable outcomes (22). Our results suggest similar outcomes.

Though our results are compelling, this study is not without its own limitations, inherent to the use of single institution, retrospective data. After excluding patients who did not meet inclusion criteria, 116 patients remained, limiting the sample size for data analysis, which could result in underpowered results. This data is also representative of the practice of a small group of thoracic surgeons at our institution and outcomes may be reflective of the practices at our institution. Additionally, our center does not automatically initiate an ID consultation following a positive culture result or diagnosis of empyema. As a result, patients with empyema who are under the primary care of thoracic surgeons at our facility often do not receive ID consultation, in contrast to those whose care is principally overseen by hospitalists. A multicenter review would allow for a greater sample size and may further show a difference in outcomes between the two groups. Another limitation of the dataset is that there are multiple ID physicians who have worked with and treated these patients over the duration of the data reviewed. Depending on the physician's training, practices of antibiotic therapy may be different compared to other ID physicians. Lastly, some patients were lost to follow-up after the 30-day period following discharge which may result in underreporting of outcomes, particularly if any complications arose after this period in those who were not tracked. Despite these limitations, our results add to the limited knowledge currently published about the adequate duration of antibiotics following source control for pleural empyema.

Conclusions

In conclusion, longer durations of antibiotics did not result in better clinical outcomes for patients with pleural empyema treated with surgical decortication. This data helps to better characterize antibiotic management in this patient population and questions whether antibiotics are being overused in the treatment of pleural empyema after source control has been obtained. Over 45 randomized control trials have been published for a variety of IDs, including community-acquired pneumonia, complicated urinary tract infection, intraabdominal infection, Gramnegative bacteremia, and osteomyelitis, and all have shown that "shorter is better" with no difference in efficacy in treatment between shorter and traditional courses of antibiotics (23-25). It is now time for the management of pleural empyema to modernize and to be driven by highlevel evidence regarding antibiotic therapy. The completion of randomized control trials is warranted and needed to better understand the optimal duration of antibiotics for pleural empyemas requiring surgical intervention.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.

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amegroups.com/article/view/10.21037/jtd-24-61/rc

Data Sharing Statement: Available at https://jtd.amegroups. com/article/view/10.21037/jtd-24-61/dss

Peer Review File: Available at https://jtd.amegroups.com/ article/view/10.21037/jtd-24-61/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-61/coif). The authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board (IRB) at Virginia Commonwealth University (No. HM20021602) and informed consent was waived for this retrospective analysis.

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Cite this article as: Freudenberger DC, Scheese D, Wolfe LG, Ramamoorthy BU, Burrell LM, Puig CA, Shah RD, Julliard WA. More isn't always better: antibiotic duration after surgical decortication in pleural empyema. J Thorac Dis 2024;16(6):3873-3881. doi: 10.21037/jtd-24-61 an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77.

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