Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
Definitions
Clinical resolution
- Complete resolution of signs and symptoms (fever, leukocytosis, hypotension, respiratory failure, and localizing symptoms) such that no further antimicrobial therapy is required; assessed at end of treatment and follow up

Adverse effects
- Mild/Moderate
  - Rash, transaminitis, altered mental status, diarrhea, nausea/vomiting, prolonged QTc without cardiac event, acute renal risk, electrolyte abnormality without cardiac/neurologic event while on therapy
- Serious
  - Clostridiodes difficile (CDI) within 90 days of discharge, development of multi-drug resistant organism (MDRO) within 90 days of discharge, anaphylaxis, rhabdomyolysis, acute renal injury/failure, seizure, drug-induced thrombocytopenia/neutropenia/anemia, Steven-Johnson-Syndrome/Toxic epidermal necrosis while on therapy

Antimicrobial optimization
- an optimal antimicrobial regimen does not have any of the following components:
  - Unnecessary
    - For noninfectious syndromes (e.g., asymptomatic bacteriuria), nonbacterial infections (e.g., viral respiratory tract infection without superimposed pneumonia), days of therapy beyond indicated duration of therapy absent of any clinical reason for lengthened course, use of redundant antimicrobial therapy (e.g., double-anaerobic coverage)
  - Inappropriate
    - Use of antimicrobial in setting of established infection to which the pathogen is resistant, or use is not concordant in institutional treatment guidelines (e.g., fluoroquinolone for cystitis when other options available)
  - Suboptimal
    - Use of antimicrobials in the setting of established infection that can be improved by drug: (1) selection, (2) route, (3) dose and interval
      - Use of overly broad agent to treat susceptible bacterium within a lesser category antimicrobial if allergies do not preclude its use
      - Use of intravenous (IV) when oral (PO) equivalent with high bioavailability is an option based on IV to PO institutional guideline
      - Dose too high or too low for infection and/or renal function

Target Disease States:
- Intra-Abdominal Infection (IAI):
  - Spontaneous bacterial peritonitis confirmed by paracentesis and polymorphonuclear leukocytes greater than or equal to 250 cells/cc.
  - Radiographic evidence of cholecystitis, cholangitis, appendicitis, diverticulitis, or abdominal abscess following surgical source control
- Urinary Tract Infection (UTI):
  - Asymptomatic bacteriuria (ASB): Antimicrobial indication for UTI and lack of documentation for urinary symptoms listed below. Appropriate antimicrobial duration for non-pregnant ASB was zero days
  - Cystitis: dysuria, supra-pubic pain, increased urinary frequency, altered mental status without other potential causes, without fever, flank pain, or other suspicious findings of pyelonephritis or complicated UTI
  - Pyelonephritis: ICD code and/or chart documentation at physician discretion
- **Complicated urinary tract infection**: all other urinary tract infection not meeting the above criteria for urinary tract infection

- **Skin/Soft Tissue Infection (SSTI)**:
  - Includes cellulitis/erysipelas, wound infection, and cutaneous abscesses assigned by ICD code and/or documentation as hospital problem

- **Respiratory Tract Infection**:
  - **Community-Acquired Pneumonia (CAP)**: Presentation of pneumonia less than 48 hours from hospital admission, with or without risk factors for multi-drug resistant organisms. Diagnosed by physician, with radiographic evidence.
  - **Hospital-associated pneumonia (HAP)**: Presentation of pneumonia greater than 48 hours from hospital admission. Diagnosed by physician, with radiographic evidence.
  - **Respiratory viral infection (RVI)**: Positive testing for a respiratory virus without radiographic evidence of pneumonia OR positive testing, radiographic findings, and procalcitonin <0.25. Appropriate antimicrobial duration for RVI is 0 days and if influenza positive, 5 days of oseltamivir.

**Excluded disease states, populations, and organisms:**

- Solid organ transplant
- Neutropenia (ANC <500 cells/cc)
- Cystic fibrosis
- HIV with CD4 <200 cells/cc
- Primary immunodeficiencies
- Age <18 years
- Discharge location hospice
- Discharge with intravenous antimicrobials
- Transferred from outside hospital
- Severe/complicated infections
  - Endocarditis
  - Meningitis/Central nervous system
  - Lack of source control
  - Febrile neutropenia
  - Prostatitis/orchitis/epididymitis
  - Osteoarticular infections
  - Diabetic foot infection
  - Necrotizing fasciitis
  - Hidradenitis suppurativa
  - Meningitis, brain abscess
  - Mediastinitis
  - Bloodstream due to fungi, *S. aureus, Enterococci*
  - Fungal pneumonia
  - Empyema, lung abscess
  - *Actinomyces* infection
  - *Aspergillus* infection
  - Mycobacterial infections
# eFigure 1. Institutional Guidelines for Antimicrobial Selection and Duration of Therapies at the Time of Intervention Implementation

| **Institutional Oral Antimicrobial Selection and Duration Guidance** | **Respiratory Tract Infections** | **Urinary Tract Infections** |
| --- | --- | --- |
| Community-acquired pneumonia, with or without risk factors (without microbiologic data) | • Amoxicillin-clavulanic acid 1000/62.5 mg 2 tabs BID + (azithromycin 500 mg daily or doxycycline 100 mg BID)  
  • Cefuroxime 500 mg BID OR cefpodoxime 400 mg BID + (azithromycin 500 mg daily or doxycycline 100 mg BID)  
  • Doxycycline 100 mg BID  
  • Moxifloxacin 400 mg OR levofloxacin 750 mg daily | Community-acquired pneumonia, with or without risk factors (without microbiologic data)  
• Doxycycline 100 mg BID  
• Azithromycin 500 mg x1 then 250 mg daily  
| Acute exacerbation of COPD (AECOPD) | • Moxifloxacin 400 mg OR levofloxacin 750 mg daily | Uncomplicated UTI/cystitis: Align with organism susceptibility  
• Nitrofurantoin (NFT) 100 mg BID  
• Sulfamethoxazole/trimethoprim (SMT) 1 DS tab BID  
• Beta-lactam (targeted to organism)  
• Fosfomycin 3 gm oral sachet (MDRO history only)  
| Hospital acquired pneumonia | | Complicated UTI/pyelonephritis Align with organism susceptibility  
• Sulfamethoxazole/trimethoprim (SMT) 1-2 DS tab BID  
• Ciprofloxacin 500 mg BID  
• Beta-lactams (targeted to organism)  
| Influenza | • Oseltamivir 75 mg BID | Asymptomatic bacteriuria  
• Do not treat if not pregnant, or perioperative prophylaxis  
| Respiratory Tract Infections | 5 days in patients with prompt clinical response 7-10 days in patients with structural lung disease or delayed response | 5 days  
| 7 days w/ prompt clinical response: tailor therapy to microbiologic data  
| 0 days | © 2022 Mercuro NJ et al. *JAMA Network Open.*
**Institutional Oral Antimicrobial Selection and Duration Guidance**

| Skin Structure Infection                  | Non-purulent cellulitis | Purulent cellulitis/cutaneous abscess (suspected MRSA) | Intra-abdominal infection |
|-------------------------------------------|-------------------------|--------------------------------------------------------|--------------------------|
| Spontaneous bacterial peritonitis         |                         |                                                       |                          |
| Complicated, community acquired intra-abdominal infection **with source control** e.g., appendicitis, cholecystitis, diverticulitis s/p removal of foci |                         |                                                       |                          |
|                                           | • Cephalexin 500 mg QID, Cefuroxime 500 mg BID | • Doxycycline 100 mg BID • Sulfamethoxazole/trimethoprim 1-2 DS BID | • Moxifloxacin 400 mg or levofloxacin 750 mg daily |
|                                           | • Dicloxacillin 500 mg QID |                                                    | • Moxifloxacin 400 mg daily • Ciprofloxacin 500 mg BID + metronidazole 500 mg BID/TID |
|                                           | • Clindamycin 300-450 mg TID (severe beta lactam allergy) |                                                    | • Cefuroxime 500 mg BID + metronidazole 500 mg BID • Amoxicillin-clavulanic acid 875/125 mg BID |
|                                           |                         |                                                    |                          |
|                                           | 5 days with prompt clinical response | 5 days with prompt clinical response | 4-7 days after source control 7 days targeted therapy in transient bacteremia after foci removed |

*Disclaimer: Guidelines for oral antimicrobial selection and duration were developed at the time of the intervention implementation. Local guidance should be considered with antibiogram and updated literature.*
eFigure 2. Nonrandomized Stepped-Wedge Diagram

5 Hospital Sites, 17 service teams

Quarter 1, Baseline
Group 1/2/3: Pre-intervention
9/2018-10/2018

Quarter 2, Phase 1 Implementation
Group 1: Post-intervention
11/2018-2/2019
Group 2/3: Pre-intervention

Quarter 3, Phase 2 Implementation
Group 1/2: Post-intervention
8/2018-10/2018
Group 3: Pre-intervention
8/2018-10/2018

Quarter 4, Phase 3 Implementation
Group 1/2/3: Post-intervention
6/2019-8/2019

1440 subjects screened retrospectively inclusion criteria

- 640 excluded*
  - 423 complicated/severe infection
  - 102 Solid organ transplant/ neutropenia
  - 96 transfer to/from outside facility or hospice
  - 47 discharged with parenteral antimicrobial
  - 7 prisoner or pregnant

*Subjects able to meet multiple exclusion criteria

Baseline
Pre-intervention: 17 service teams (n=125)
Post-intervention: 0 service teams (n=0)

Phase 1
Pre-intervention: 11 service teams (n=200)
Post-intervention: 6 service teams (n=100)

Phase 2
Pre-intervention: 4 service teams (n=75)
Post-intervention: 13 service teams (n=150)

Phase 3
Pre-intervention: 0 service teams (n=0)
Post-intervention: 17 service teams (n=150)

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Lighter shades denote pre-intervention periods, darker shades denote post-intervention period.
Phase 1 (n=250) consisted of units from academic medical center only, overall mean difference in optimal prescribing between pre- and post-intervention periods +26.2%
Phase 2 (n=275) consisted of units from both academic and community medical centers, overall mean difference in optimal prescribing between pre- and post-intervention periods +43.1%
Phase 3 (n=275) consisted of units from community medical centers, overall mean difference in optimal prescribing between pre- and post-intervention periods +44.4%
**eTable 1. Expanded Demographics and Patient Characteristics**

|                                | Overall Pre- (n=400) | Overall Post- (n=400) | Phase 1 Pre- (n=25) | Phase 1 Post- (n=225) | Phase 2 Pre- (n=150) | Phase 2 Post- (n=125) | Phase 3 Pre- (n=225) | Phase 3 Post- (n=50) |
|--------------------------------|----------------------|----------------------|---------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| Age, years (± SD)              | 69.0 (17.1)          | 64.5 (17.2)          | 55.9 (18.9)         | 61.7 (17.5)          | 64.6 (15.7)          | 66 (16.7)            | 73.4 (16.4)          | 73.6 (13.4)          |
| Female sex, n (%)              | 221 (55.3)           | 220 (55)             | 128 (56.9)          | 11 (44)              | 81 (54)              | 69 (55.2)            | 129 (57.3)           | 23 (46)              |
| Race, n (%)                    |                      |                      |                     |                      |                      |                      |                      |                      |
| • Black                        | 113 (28.2)           | 200 (50)             | 16 (64)             | 142                   | 71 (47.3)            | 52 (41.6)            | 26 (11.6)            | 6 (12)               |
| • White                        | 259 (64.8)           | 161 (40.3)           | 6 (24)              | 63.1 (3.6)            | 65 (43.3)            | 58 (46.4)            | 188 (83.6)           | 43 (86)              |
| • Other/unknown                | 28 (7)               | 39 (9.7)             | 3 (12)              | 60 (26.7)             | 23 (10.2)            | 14 (8.6)             | 15 (12)              | 11 (4.8)             |
| Charlson Score, median (IQR)   | 2 (1-3)              | 2 (1-3)              | 1 (0-3)             | 1 (1-3)               | 3 (2-4)              | 3 (3-5)              | 4.2 (2.3)            | 4.1 (3.1)            |
| SIRS ≥2 on day 1, n (%)        | 116 (29)             | 134 (33.5)           | 13 (52)             | 86 (38.2)             | 28 (18.7)            | 37 (29.8)            | 75 (33.3)            | 11 (22)              |
| SIRS ≥2 on day 3, n (%)        | 22 (5.5)             | 18 (4.5)             | 1 (4)               | 11 (4.9)              | 5 (3.3)              | 4 (3.2)              | 16 (7.1)             | 3 (6)                |
| Length of stay, days (± SD)    | 3.6 (2.2)            | 3.3 (2.2)            | 3.0 (1.5)           | 3.4 (1.9)             | 3.5 (2.2)            | 4.0 (2.3)            | 3.9 (2.4)            | 3.7 (3.0)            |
| Any MDRO risk factor, n (%)    |                      |                      |                     |                      |                      |                      |                      |                      |
| • Admit in last 90 days        | 216 (54)             | 210 (52.5)           | 10 (40)             | 117 (52)              | 86 (57.3)            | 62 (49.6)            | 120 (53.3)           | 31 (62)              |
| • Antimicrobial in last 90 days| 130 (32.5)           | 117 (29.3)           | 9 (36)              | 61 (27.1)             | 49 (32.7)            | 38 (30.4)            | 72 (32)              | 18 (36)              |
| • Prior MDRO colonization      | 144 (36)             | 154 (38.5)           | 8 (32)              | 82 (36.4)             | 55 (36.7)            | 45 (36)              | 81 (36)              | 27 (54)              |
| • Immunocompromised            | 22 (5.5)             | 27 (6.8)             | 2 (8)               | 13 (5.8)              | 8 (5.3)              | 10 (8)               | 12 (5.3)             | 4 (8)                |
| • Non-ambulatory status        | 7 (1.8)              | 15 (3.8)             | 1 (4)               | 12 (5.3)              | 1 (0.7)              | 3 (2.4)              | 5 (2.2)              | 0                    |
| Pneumonia, n (%)               | 144 (36)             | 120 (30)             | 6 (24)              | 64 (28.4)             | 45 (30)              | 39 (31.2)            | 93 (41.3)            | 17 (34)              |
| • CAP without risk factors     | 108 (27)             | 92 (23)              | 3 (12)              | 48 (21.3)             | 39 (26)              | 30 (24)              | 66 (29.3)            | 14 (28)              |
| • CAP with risk factors        | 33 (8.3)             | 24 (6)               | 2 (8)               | 13 (5.8)              | 6 (4)                | 8 (6.4)              | 25 (11.1)            | 3 (6)                |
| • HAP                          | 3 (0.8)              | 4 (1)                | 1 (4)               | 3 (1.3)               | 0                    | 1 (0.8)              | 2 (0.9)              | 0                    |
| AECOPD/ upper respiratory tract infection, n (%) | 101 (25.3) | 113 (28.2) | 2 (8) | 64 (28.4) | 43 (28.7) | 39 (31.2) | 56 (24.9) | 10 (20) |

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| Infection Type | Overall Pre- (n=400) | Overall Post- (n=400) | Phase 1 Pre- (n=25) | Phase 1 Post- (n=225) | Phase 2 Pre- (n=150) | Phase 2 Post- (n=125) | Phase 3 Pre- (n=225) | Phase 3 Post- (n=50) |
|----------------|----------------------|-----------------------|--------------------|----------------------|--------------------|----------------------|--------------------|--------------------|
| Urinary tract infection (UTI) | | | | | | | | |
| • Pyelonephritis | 115 (28.7) | 88 (22) | 6 (24) | 44 (19.6) | 42 (28) | 32 (25.6) | 67 (29.8) | 12 (24) |
| • Complicated UTI | 25 (6.3) | 23 (5.8) | 3 (12) | 12 (5.3) | 8 (5.3) | 10 (8) | 14 (6.2) | 1 (2) |
| • Cystitis | 46 (11.5) | 39 (9.8) | 1 (4) | 22 (9.8) | 16 (10.7) | 11 (8.8) | 29 (12.9) | 6 (12) |
| Skin/soft tissue infection | | | | | | | | |
| • Purulent | 44 (11) | 26 (6.5) | 2 (8) | 10 (4.4) | 18 (12) | 11 (8.8) | 24 (10.7) | 5 (10) |
| • Non-purulent | 53 (13.3) | 72 (18) | 11 (44) | 49 (21.8) | 22 (14.7) | 13 (10.4) | 20 (8.9) | 10 (20) |
| Intra-abdominal infection | 4 (1) | 12 (3) | 0 (0) | 9 (4) | 2 (1.3) | 3 (2.4) | 2 (0.9) | 0 |
| Disposition, n (%) | | | | | | | | |
| • Home/home services | 328 (82) | 345 (86.3) | 21 (84) | 193 (85.8) | 128 (85.3) | 111 (88.8) | 179 (79.6) | 41 (82) |
| • Long-term care facility/ skilled nursing facility | 69 (17.3) | 51 (12.8) | 4 (16) | 85.8 | 22 (14.7) | 14 (11.2) | 43 (19.1) | 9 (18) |
| • Left against medical advice | 3 (0.8) | 4 (1) | 0 (0) | 4 (1.8) | 0 (0) | 0 (0) | 3 (1.3) | 0 (0) |

AECOPD - acute exacerbation of chronic obstructive pulmonary disorder
### eTable 2. Expanded Patient Outcomes

|                        | Overall Pre- (n=400) | Overall Post- (n=400) | Phase 1 Pre- (n=25) | Phase 1 Post- (n=225) | Phase 2 Pre- (n=150) | Phase 2 Post- (n=125) | Phase 3 Pre- (n=225) | Phase 3 Post- (n=50) |
|------------------------|----------------------|-----------------------|---------------------|-----------------------|----------------------|----------------------|----------------------|----------------------|
| Optimized discharge regimen | 144 (36)            | 326 (81.5)            | 14 (56)             | 185 (82.2)            | 59 (39.3)            | 103 (82.4)           | 71 (31.6)            | 38 (76)              |
| 30-day mortality | 3 (0.8)              | 6 (1.5)               | 0 (0)               | 3 (1.3)               | 0 (0)                | 3 (2.4)              | 3 (1.3)              | 0                    |
| 90-day mortality | 12 (3)               | 11 (2.8)              | 1 (4)               | 6 (2.7)               | 4 (2.7)              | 4 (3.2)              | 7 (3.1)              | 1 (2)                |
| 30-day readmission | 77 (19.3)            | 81 (20.3)             | 4 (16)              | 38 (16.9)             | 28 (18.7)            | 28 (22.4)            | 45 (20)              | 15 (30)              |
| • Infection related | 33 (8.3)             | 21 (5.3)              | 3 (12)              | 14 (6.2)              | 10 (6.7)             | 4 (3.2)              | 20 (8.9)             | 3 (6)                |
| Clinical resolution | 253/303              | 241/275               | 13/17               | 130/153               | 82/96                | 78/88                | 158/190              | 33/34                |
|                       | (83.5)               | (87.6)                | (76.5)              | (85)                  | (85.4)               | (88.6)               | (83.2)               | (97.1)               |
| Any adverse drug event | 78 (19.8)            | 53 (13.6)             | 8 (32)              | 32 (14.4)             | 20 (13.4)            | 17 (13.9)            | 50 (22.7)            | 4 (8.5)              |
| Severe adverse drug event (all) | 36 (9)               | 13 (3.3)              | 6 (24)              | 8 (3.6)               | 8 (5.3)              | 4 (3.2)              | 22 (9.8)             | 1 (2)                |
| • C. difficile | 7 (1.8)              | 2 (0.5)               | 3 (12)              | 1 (0.4)               | 0                    | 0                    | 4 (1.8)              | 1 (2)                |
| • MDRO* at 90 days | 28 (7)               | 10 (2.5)              | 3 (12)              | 6 (2.7)               | 7 (4.7)              | 4 (3.2)              | 18 (8)               | 0                    |

*Multi-drug resistant organism

Phases 1, 2, 3 represent three groups of hospital service teams, implemented in accordance to the stepped wedge design.
eTable 3. Differences in Antimicrobial Length of Therapy (Mean Days)

|                          | Unadjusted                                      | Time Adjusted Estimates |
|--------------------------|-------------------------------------------------|-------------------------|
|                          | Pre-    | Post-   | Absolute % Difference (95% CI) | P-value | Pre-   | Post-  | Absolute % Difference (95% CI) | P-value |
| Total (n=800)            | 8.9     | 7.4     | -1.5 (-1.9 to -1.0)            | <0.001  | 8.7    | 7.6    | -1.1 (-1.7 to -0.6)            | <0.001  |
| Outpatient (n=800)       | 5.5     | 4.6     | -0.9 (-1.3 to -0.6)            | <0.001  | 5.3    | 4.8    | -0.5 (-1.0 to 0.0)             | 0.05    |
| Total, Respiratory infection (n=455) | 8.3  | 6.4     | -1.9 (-2.3 to -1.4)            | <0.001  | 8.2    | 6.5    | -1.8 (-2.3 to -1.2)            | <0.001  |
| Total, Urinary tract infection (n=203) | 9.7  | 8.1     | -1.6 (-2.6 to -0.6)            | 0.002   | 9.4    | 8.5    | -0.9 (-2.2 to 0.4)             | 0.16    |
| Total, Skin/soft tissue infection (n=125) | 9.7  | 9.8     | 0.0 (-1.2 to 1.3)              | 0.94    | 9.5    | 10.0   | +0.5 (-1.2 to 2.2)             | 0.58    |

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eTable 4. Work Flow of Intervention for Antimicrobial Stewardship and/or Clinical Pharmacist

|                                | Base TOC model                                                                 | Modifications made to optimize process for individual practice setting |
|--------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|
| **Identifying patients approaching discharge** | • Electronic medical record included datapoints for anticipated discharge date  
• Patients approaching discharge on antimicrobials discussed on collaborative rounds | • Daily reports obtained from case managers  
• Nursing managers contacted on individual units for upcoming discharges  
• Outpatient pharmacy contacted inpatient pharmacy team for new prescriptions for oral antimicrobials on patients who do not have a documented antibiotic discharge plan |
| **Patient therapy assessments** | • Institutional guidelines applied  
• Prospective audit and feedback of patients with active antimicrobials conducted weekdays daily 7am-4pm  
• Clinical assessments conducted on inpatient and discharge antimicrobial therapy | • Weekday assessments conducted by either antimicrobial stewardship or clinical pharmacist, depending on resources and care model  
• Weekend assessments conducted by antimicrobial stewardship, or not performed, depending on care model |
| **Communication** | • Individual cases discussed during collaborative rounds  
• Therapy plan documented in progress notes after confirmation with team | • Paging or phone call communication in non-rounding models |
| **Discharge order entry** | • Orders entered into discharge queue for cosigning by primary team (prior to discharge) with stop date  
• Orders modified in discharge queue during rounds, if needed | • Paging or phone call to prescriber to review/modify the discharge prescription, if needed, when discharge orders have already been entered. Timely discharge of the patient was prioritized and the ability to conduct the intervention was designed to not interfere with or delay the discharge process |