Guidelines for Treatment of Respiratory Infections due to Nontuberculous Mycobacteria

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ESGMYC Recommendations for Mycobacterial Infections

Disclosures

Alere™ provided the participating centres with blood-collecting tubes for the OPTIMIST clinical trial, of which I am the promoter

NTM-PD

-Emerging infection

-Poor response to chemotherapy (surgery)

-Guidance for management (expert opinion)

(BTS 1999, ATS/IDSA 2007)

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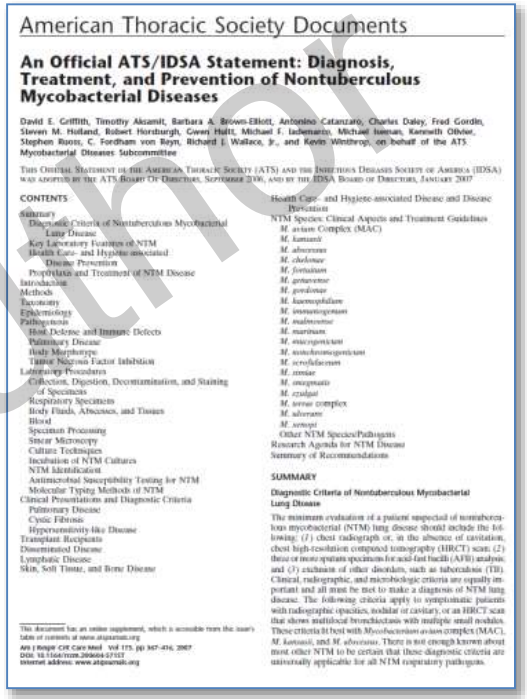
ATS/IDSA/ERS/ESCMID Guidelines



American Thoracic Society Documents

An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases

David E. Griffith, Timothy Aksamit, Barbara A. Brown-Elliott, Antonino Catanzaro, Charles Daley, Fred Gordin, Steven M. Holland, Robert Horsburgh, Gwen Huitt, Michael F. Iademarco, Michael Iseman, Kenneth Olivier, Stephen Ruoss, C. Fordham von Reyn, Richard J. Wallace, Jr., and Kevin Winthrop, on behalf of the ATS Mycobacterial Diseases Subcommittee

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SUMMARY

Diagnostic Criteria of Nontuberculous Mycobacterial Lung Disease

The minimum evaluation of a patient suspected of nontuberculous mycobacterial (NTM) lung disease should include the following: (*1*) chest radiograph or, in the absence of cavitation, chest high-resolution computed tomography (HRCT) scan; (*2*) three or more sputum specimens for acid-fast bacilli (AFB) analysis; and (*3*) exclusion of other disorders, such as tuberculosis (TB). Clinical, radiographic, and microbiologic criteria are equally important and all must be met to make a diagnosis of NTM lung disease. The following criteria apply to symptomatic patients with radiographic opacities, nodular or cavitary, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules. These criteria fit best with *Mycobacterium avium* complex (MAC), *M. kansasii*, and *M. abscessus*. There is not enough known about most other NTM to be certain that these diagnostic criteria are universally applicable for all NTM respiratory pathogens.

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Am J Respir Crit Care Med Vol 175. pp 367–416, 2007
DOI: 10.1164/rccm.200604-571ST
Internet address: www.atsjournals.org

Outline

- ✓ Management of NTM-PD
- ✓ The GRADE Approach
- ✓ ATS/IDSA/ERS/ESCMID Guidelines

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M. avium complex

Pre-Macrolide

-Response: 27-30% with RMP (BTS)

Macrolide

-Very active (resistance in monotherapy!)

-Response: 60%-65% (multi-D macrolide-based regimens)

M. avium complex

The Guidelines say...

	Nodular /bronchiectasis	Fibrocavitary	Macrolide-R
ATS/IDSA (2007)	-Three-times-wkly macrolide-RE -Duration: 12 months CN *(A, II)*	-Daily macrolide-RE (+/- injectable agent) -Duration: 12 months CN *(B, II)*	Expert consultation
van Ingen (2013)	-Daily macrolide-RE (+/- AS) -Duration: >12 months CN -Alternative: macrolide-CloE		---

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ATS/IDSA. *Am J Respir Crit Care Med 2007;175:367-416*
van Ingen. *Expert Rev Anti Infect Ther 2013;11:1065-77*

M. kansasii

-Treatment of MK-PD resembles that of MTb

-<u>Response</u>:

-Pre-RMP: 50%-80% (high relapse rates)

-93%-98% with RMP-based regimens*

-*In vitro* activity of Clarithromycin and Moxifloxacin

-Successful experience with Clarithromycin**

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*__Ahn.__ *Am Rev Respir Dis 1983;* __*Santin*__*. Eur Respir J 2009.*
**__*Shitrit*__*. Chest 2006;* __*Griffith*__*. Clin Infect Dis 2003.*

M. kansasii

The Guidelines say...

	RMP-Susceptible	RMP-R
ATS/IDSA (2007)	-Daily HRE -Duration: 12 months CN *(A, II)*	-Three-drug regimen including: macrolide, moxi, and EMB, STX or streptomycin *(A, II)*
van Ingen (2013)	-Daily HRE (+/- AS) -Duration: >12 months CN -Alternative: macrolide-RE	---

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M. abscessus

-Resistance to anti-tuberculous drugs

-Susceptible to Clarithromycin (untreated)

-Amik (90%), Cefox (70%), Imipen (50%), Linez and Tigec

-Treatment recommendations based on *in vitro* tests

-Surgery improves cure rates (57% vs 28%)*

**Jarand J 2011*

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M. abscessus

The Guidelines say...

ATS/IDSA (2007)	-Limited (focal) disease: Surgical resection and multi-D therapy *(A, II)* -Control symptoms and progression: Periodic multi-D therapy *(C, III)*

Koh WJ (2011) (Clarithro, Cipro, Doxi, Amik, Cefoxitin)

- 12 months CC: 25% *M. abscessus* vs. 88% *M. massiliense*

Harada T (2012)

-12 months CC: 31% *M. abscessus* vs. 50% *M. massiliense*

Park J (2017) (Clarithro, Cipro, Doxi, Amik, Cefoxitin/Imipenem)

-12 months CC: 26% *M. abscessus* vs. 82% *M. massiliense*

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M. abscessus

The Guidelines say...

ATS/IDSA (2007)	-Limited (focal) disease: Surgical resection and multi-D therapy *(A, II)* -Control symptoms and progression: Periodic multi-D therapy *(C, III)*
van Ingen (2013)	*M. abscessus* subsp. *abscessus* and subsp. *bolletii* -Three or four of: Amik, Cefox, Imipen, Tigec, Linez (intensive phase). Duration: >12 months CN *M. abscessus* subsp. *massiliense* -Macrolide + two of: Amik, Cefox, Imipen, Tigec, Linez (intensive phase) Duration: >12 months CN

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ATS/IDSA. *Am J Respir Crit Care Med 2007;175:367-416*
van Ingen. *Expert Rev Anti Infect Ther 2013;11:1065-77*

M. xenopi

-Co-morbidity frequent

-Cure at 5 years:

  -BTS Trial (2001): 24% (RE), 10% (HRE) alive and cured

  -BTS Trial (2008): 12% (Cipro.), 18% (Clarithro.) alive and cured

-**Andréjak C (France 2009)**: median survival 16 months (69% dead at 3 years). Cure: 21%

-**van Ingen J (Netherlands 2008)**: 26% culture conversion

M. xenopi

The Guidelines say...

ATS/IDSA (2007)	-The optimal treatment and duration of M. Xenopi-PD has not been well established -Daily RE-Clarithromycin -Duration: 12 months CN
van Ingen (2013)	-Daily RE-macrolide (+/- quinolone) -Alternative: RE-quinolone -Duration: 12 months CN

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This Official Statement of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) was adopted by the ATS Board Of Directors, September 2006, and by the IDSA Board of Directors, January 2007

CONTENTS

TABLE 1. THE STRENGTH OF RECOMMENDATIONS BASED ON QUALITY OF EVIDENCE (ADAPTED FROM THE INFECTIOUS DISEASE SOCIETY OF AMERICA/UNITED STATES PUBLIC HEALTH SERVICE RATING SYSTEM)

Categories Reflecting the Strength of Each Recommendation for or against Its Use		Grades Reflecting the Quality of Evidence on Which Recommendations Are Based	
Category	Definition	Grade	Definition
A	Good evidence to support a recommendation for use	I	Evidence from at least one properly randomized, controlled trial
B	Moderate evidence to support a recommendation for use	II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies or from dramatic results in uncontrolled experiments
C	Poor evidence to support a recommendation for or against use	III	Evidence from opinion of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
D	Moderate evidence to support a recommendation against use		
E	Good evidence to support a recommendation against use		

Diagnostic Criteria of Nontuberculous Mycobacterial Lung Disease

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ATS/IDSA/ERS/ESCMID Guidelines

GRADE system
Grading
Recommendations
Assessment
Development
Evaluation

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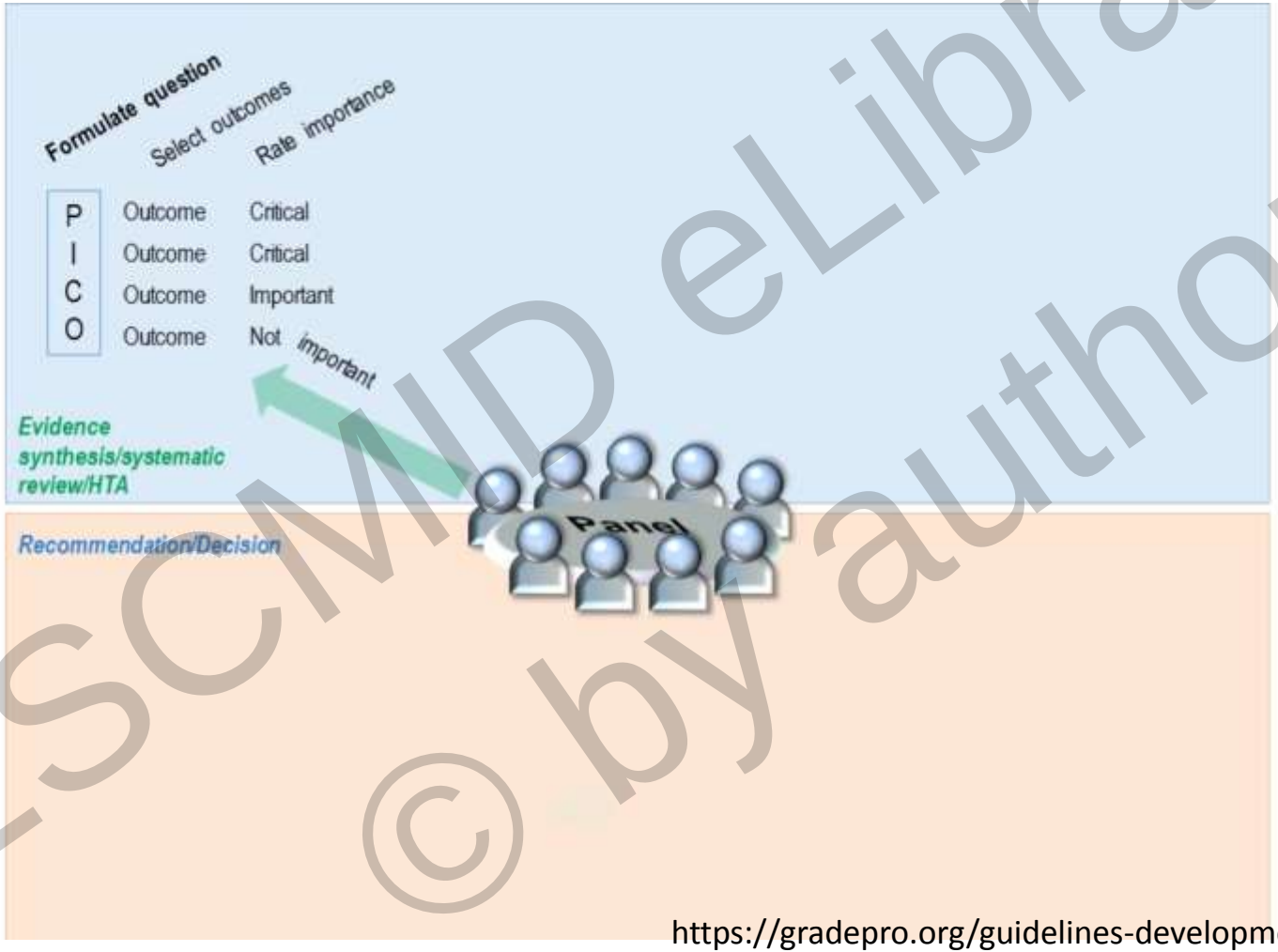
Certainty of Evidence/Strength of Recommendation

Certainty of Evidence		Definition
High	⨁⨁⨁⨁	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	⨁⨁⨁◯	Further research is likely to have an important impact on our confidence in the effect and may change the estimate
Low	⨁⨁◯◯	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	⨁◯◯◯	Any estimate of effect is very uncertain
Strength of Recommendation		**Definition**
Strong		The Guideline Development Group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects
Conditional (weak)		The Guideline Development Group concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects



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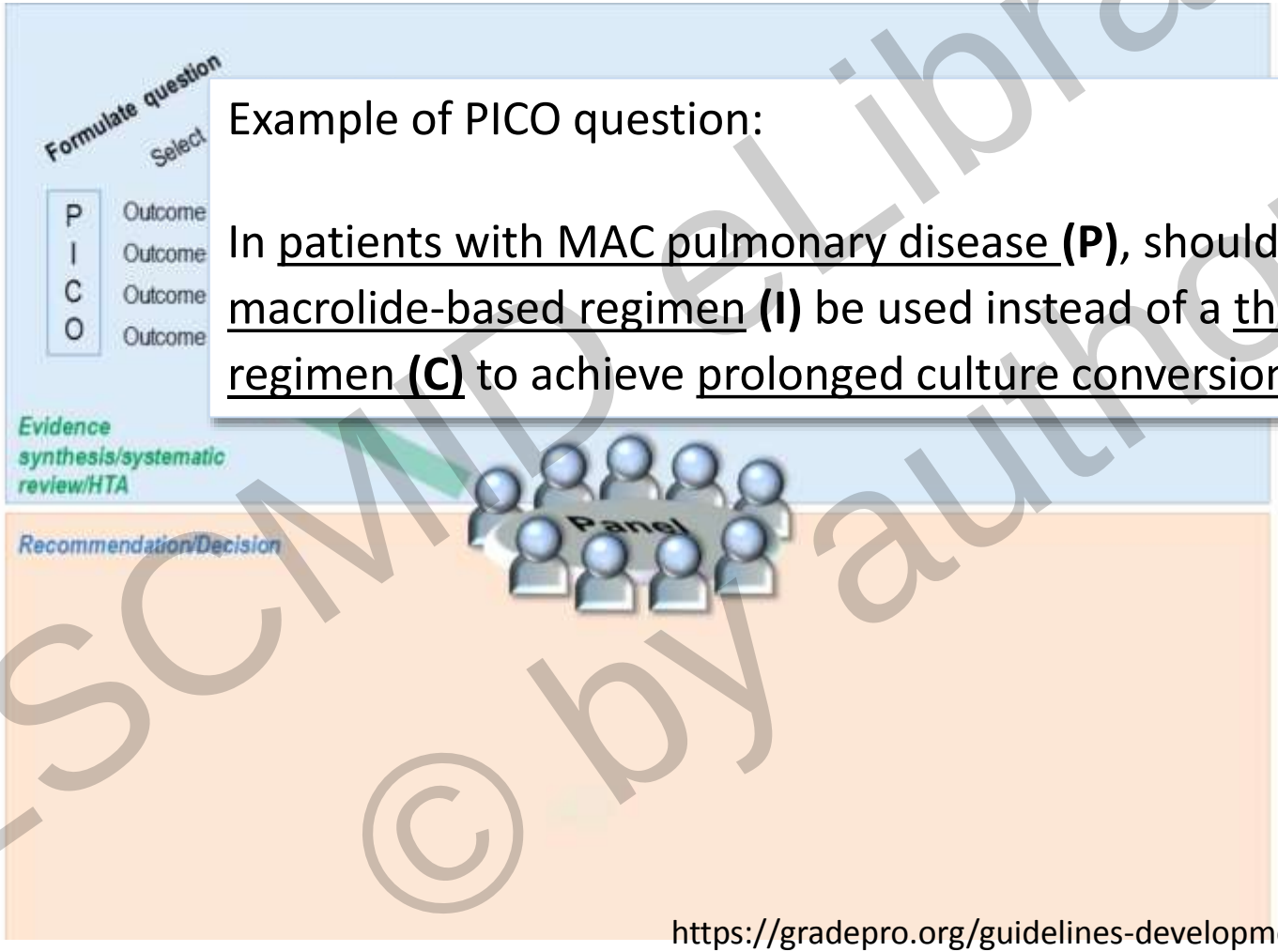

Example of PICO question:

In <u>patients with MAC pulmonary disease</u> **(P)**, should a <u>two-drug macrolide-based regimen</u> **(I)** be used instead of a <u>three-drug regimen</u> **(C)** to achieve <u>prolonged culture conversion</u> **(O)**?

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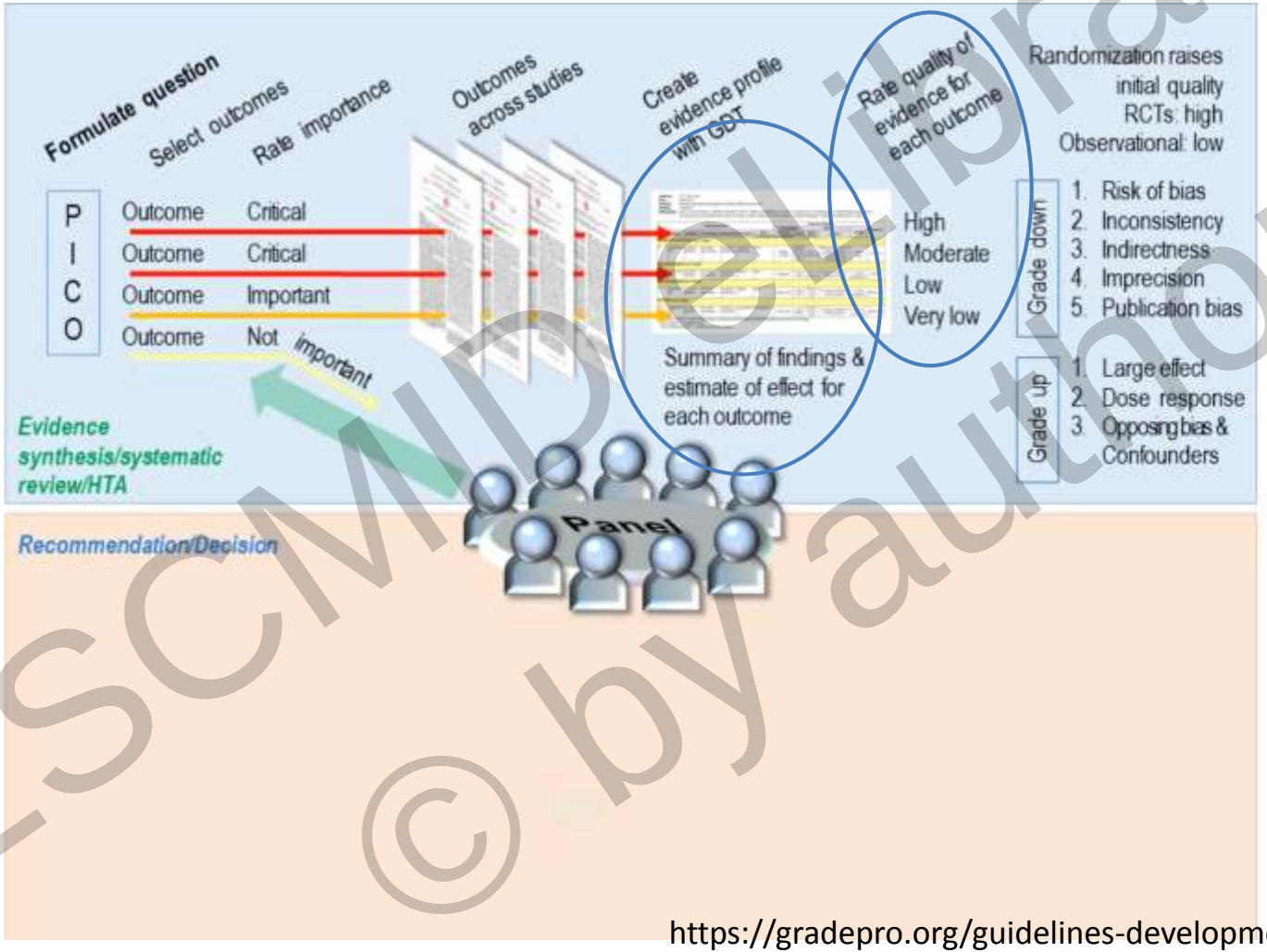

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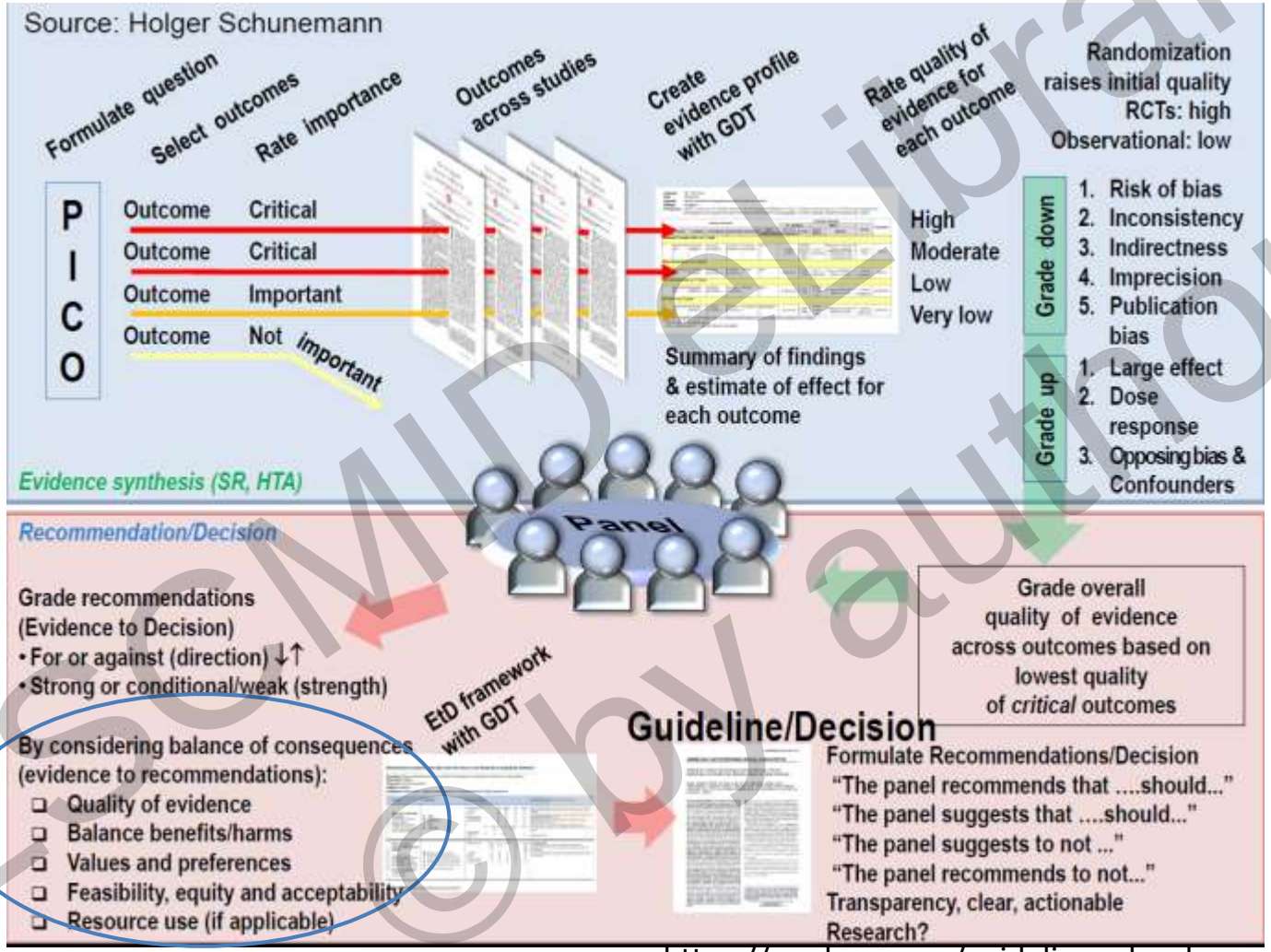

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ATS/IDSA/ERS/ESCMID Guidelines

- **21 PICO Questions**
- **Outcomes:** Cure, Death, Recurrence, Culture conversion, Adverse reactions, Serious adverse event, QoL, Resistance
- **Evidence:** Low to very low certainty

ATS/IDSA/ERS/ESCMID Guidelines
PICO Questions

- **MAC**
  - Should **3 drugs w/ macrolide** vs. **2 drugs w/ macrolide** be used for **MAC**?
  - Should **3 drugs with macrolide** vs. **3 drugs without macrolide** be used for **MAC**?
  - Should **Azithromycin** vs. **Clarithromycin** be used for **MAC**?
  - Should **daily macrolide-based regimen** vs. **3 times weekly regimen** be used for **MAC**?
  - Should **Parenteral** vs. **No parenteral agent** be used for **MAC**?
  - Should **Inhaled antibiotics** vs. **no inhaled antibiotics** be used for **MAC**?
  - Should **<12 months** vs. **>12 months** be used for **MAC**?

ATS/IDSA/ERS/ESCMID Guidelines

PICO Questions

- ***M. kansasii***
  - –Should **<12 months** vs. **>12 months** be used for ***M. kansasii***?
  - –Should **INH** vs. **no INH** be used for ***M. kansasii***?
  - –Should **daily regimens** vs. **3 times weekly regimens** be used for ***M. kansasii***?
  - –Should **Fluorquinolone** vs. **no Fluoroquinolone** be used for ***M. kansasii***?
  - –Should **Parenteral** vs. **No parenteral agent** be used for ***M. kansasii***?
- ***M. xenopi***
  - –Should **<12 months** vs. **>12 months** be used for ***M. xenopi***?
  - –Should **Two** vs. **Three drugs** be used for ***M. xenopi***?
  - –Should **a FQ-containing regimen** vs. **regimens without a FQ** be used for patients with newly diagnosed pulmonary ***M. xenopi***?
  - –Should **Parenteral** vs. **no parenteral agent** be used for ***M. xenopi***?

ATS/IDSA/ERS/ESCMID Guidelines.

PICO Questions

- ***M. abscessus***
  - –Should **two drugs** vs. **three drugs** be used for ***M. abscessus***?
  - –Should **Macrolide** vs. **No macrolide** be used for ***M. abscessus***?
  - –Should **shorter therapy** vs. **longer therapy** be used for ***M. abscessus***?
- **NTM-PD (all species)**
  - –Should **any treatment** vs. **watchful waiting** be used for **NTM**?
  - –Should **empiric treatment** vs. **culture-based treatment** be used for **NTM**?
  - –Should **Surgery** vs. **No surgery** be used for **NTM**?

ATS/IDSA/ERS/ESCMID Guidelines

The Panel

Charles Daley (ATS) (Chair)	**Emmanuelle Cambau (ESCMID)**
David Griffith (ATS)	**Erik Böttger (ESCMID)**
Ted Marras (ATS)	**Lorenzo Guglielmetti (ESCMID)**
Kenneth Olivier (ATS)	**Miguel Santin (ESCMID)**
Richard Wallace (ATS)	**Christoph Lange (ERS)**
Steven M. Holland (IDSA)	**Claire Andrejak (ERS)**
Gwen Huitt (IDSA)	**Dirk Wagner (ERS)**
Kevin Winthrop (IDSA)	**Jakko van Ingen (ERS)**
Jason Stout (IDSA)	
Methodologists (GRADE)	**Ad hoc expert**
Jan Brozek	Enrico Tortoli
Jon Iaccarino	

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IDSA Infectious Diseases Society of America

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ERS EUROPEAN RESPIRATORY SOCIETY

British Thoracic Society Guidelines for the Diagnosis and Management of Non-tuberculous Mycobacterial Pulmonary Disease (NTM-PD)

Available at:

https://www.brit-thoracic.org.uk/standards-of-care/guidelines/bts-guidelines-for-non-tuberculous-mycobacteria/

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